HYBRID POLYMERS AND METHODS OF MAKING THE SAME

INTRODUCTION

[0001] A variety of approaches have been developed to permit the sustained release of drugs in a patient. These controlled release systems achieve a number of goals, including protecting the drug from the biological environment prior to delivery, and permitting the controlled release of the drug to a targeted area.

[0002] A number of conventional controlled release systems are based on solid microstructures, such as lipospheres, liposomes, microcapsules, microparticles, and nanoparticles. The microstructures are typically introduced into the body of a subject in the form of a dispersion.

[0003] Conventional controlled delivery systems may also be prepared as solid macrostructures. An active agent, such as a drug, may be blended with a polymer. The blend may then be shaped into a specific form such as a cylinder, disc or fiber for implantation. The drug delivery system is then typically inserted into the body through an incision. These incisions are often larger than desired and may lead to a reluctance on the part of the subject to accept such a treatment. Additionally, a solid foreign body may produce irritation or discomfort in the patient, since the shape of the structure does not conform to the surrounding tissues.

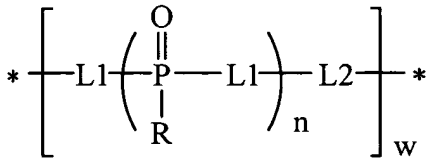
[0004] An improved delivery method that avoids the use of solvents and excipients that promote adverse reactions in patients is needed. Furthermore, a therapeutic regimen using a formulation that reduces the frequency and cost of drug treatments, and possibly reduces the need for conjoint therapies that have more severe side effects would increase the attractiveness and convenience of many controlled release therapies.

SUMMARY

[0005] In part, the present invention is directed to a biocompatible polymer, and methods of making and using the same.

[0006] In part, the present invention is directed to a composition comprising a biocompatible polymer and a biologically active agent, methods for treatment using the subject composition, and methods of making and using the same.

[0007] In part, the biocompatible polymer of the present invention has the following general formula:



wherein the properties of the polymer such as, for example, crystallinity can be adjusted by adjusting the ratio of the components L1, L2, and -P(O)(R)-.

[0008] In certain embodiments, administration of a subject composition results in sustained release of an encapsulated biologically active agent for a period of time and in an amount that is not possible with other modes of administration of the biologically active agent. In certain embodiments, such administration results in systemic levels of the biologically active agent in vivo for a prolonged period.

[0009] The subject compositions, and methods of making and using the same, achieve a number of desirable results and features, one or more of which (if any) may be present in any particular embodiment of the present invention: (i) a single dose of a subject composition may achieve the desired therapeutically beneficial response through sustained release of a biologically active agent; (ii) sustained release of a biologically active agent from a composition comprising a biocompatible and possibly biodegradable polymer; (iii) novel treatment regimens for treating or preventing diseases or conditions not limited to cancer using the subject compositions for sustained delivery of a biologically active agent; (iv) detectable systemic levels of a biologically active agent for a period of time in a patient; (v) high levels of loading (by weight), e.g. greater than 10% and up to 60% or more, of a biologically active agent in the subject compositions; (vi) lyophilization or subjection to an appropriate drying technique such as spray drying of the subject compositions and subsequent rehydration; (viii) co-encapsulation of therapeutic agents in the subject polymers.

[0010] In one aspect, the subject compositions may be biocompatible, biodegradable or both. In certain embodiments, the subject compositions contain phosphorus linkages, including, for example, phosphate, phosphonate and phosphite. In other embodiments, the monomeric units of the present invention have the structures described in the claims appended below, which are hereby incorporated by reference in their entirety into this Summary. In the subject compositions, and in particular in those embodiments containing a phosphorus linkage, the chemical structure of certain of the monomeric units may be varied to achieve a variety of desirable physical or chemical characteristics, including for example, release profiles or handling characteristics of the resulting polymer composition.

[0011] In certain embodiments, other materials may be encapsulated in the subject polymer in addition to a biologically active agent to alter the physical and chemical properties of the resulting polymer, including for example, the release profile of the resulting polymer composition. Examples of such materials include biocompatible plasticizers, delivery agents, fillers and the like.

[0012] The present invention provides methods of making the subject compositions. Examples of such methods include those described in the Exemplification below.

[0013] In another aspect, the present invention is directed to methods of using the subject compositions for prophylactic or therapeutic treatment. In certain instances, the subject compositions may be used to prevent a disease or condition. In certain embodiments, use of certain of the subject compositions, which release in a sustained manner a biologically active agent, allow for different treatment regimens than are possible with other modes of administration of such biologically active agent.

[0014] In another aspect, the efficacy of treatment using the subject compositions may be compared to treatment regimens known in the art in which the biologically active agent is not encapsulated within a subject polymer or another polymeric material. In still other aspects, the present invention is directed to a method for formulating polymers of the present invention in a pharmaceutically acceptable carrier.

[0015] In another aspect, compositions of the present invention may be spray dried and subsequently rehydrated for ready use or injected as powder using appropriate powder injecting device.

[0016] In another aspect, compostions of the present invention may be in the form of a liquid, a film, a drug loaded film, a coating for medical devices, a drug loaded coating for a medical device, or a drug loaded medical device.

[0017] In other embodiments, this invention contemplates a kit including subject compositions, and optionally instructions for their use. Uses for such kits include, for example, therapeutic applications. In certain embodiments, the subject compositions contained in any kit have been lyophilized and require rehydration before use.

[0018] These embodiments of the present invention, other embodiments, and their features and characteristics, will be apparent from the description, drawings and claims that follow.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Figure 1 shows the Mw change of degrading different subject polymers.

[0020] Figure 2 depicts mass loss of different subject polymers.

[0021] Figure 3 shows Tg change of different subject polymers.

DETAILED DESCRIPTION

1. Overview

[0022] The present invention relates in part to a new type of biocompatible polymer having phosphorus linkages. The properties of the subject compositions may be varied depending on the chemical identity of the different repeating units found in the polymer. The present invention relates in part to pharmaceutical compositions for the delivery of a biologically active agent to achieve a beneficial therapeutic effect for a patient. In certain embodiments, biocompatible and optionally biodegradable polymers may be used to achieve sustained release of an encapsulated biologically active agent. The present invention also relates to methods of administering such pharmaceutical compositions, e.g., as part of a treatment regimen, for example, subcutaneously, intravenously, or intramuscularly.

[0023] In certain aspects, the pharmaceutical compositions, upon contact with body fluids including blood, spinal fluid, lymph or the like, release the encapsulated drug over a sustained or extended period as compared to the release from an isotonic saline solution. The subject compositions may be administered as is necessary depending on the subject being treated, the severity of the affliction, the judgment of the prescribing physician, and the like.

2. Definitions

[0024] For convenience, before further description of the present invention, certain terms employed in the specification, examples, and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art.

[0025] The articles "a" and "an" are used herein to refer to one or to more than one (i.e. to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0026] The term "antineoplastic" is art-recognized, and describes therapeutic agents including agents that prevent the development, maturation, or spread of cells characterized by abnormal malignant growth, e.g., for treating or preventing cancer.

[0027] The terms "biocompatible polymer" and "biocompatibility" when used in relation to polymers are art-recognized. For example, biocompatible polymers include polymers that are neither themselves toxic to the host (e.g., an animal or human), nor degrade (if the polymer degrades) at a rate that produces monomeric or oligomeric subunits or other byproducts at toxic concentrations in the host. In certain embodiments of the present invention, biodegradation generally involves degradation of the polymer in an organism, e.g., into its monomeric subunits, which may be known to be effectively non-toxic. Intermediate oligomeric products resulting from such degradation may have different toxicological properties, however, or biodegradation may involve oxidation or other biochemical reactions that generate molecules other than monomeric subunits of the polymer. Consequently, in certain embodiments, toxicology of a biodegradable polymer intended for in vivo use, such as implantation or injection into a patient, may be determined after one or more toxicity analyses. It is not necessary that any subject

composition have a purity of 100% to be deemed biocompatible; indeed, it is only necessary that the subject compositions be biocompatible as set forth above. Hence, a subject composition may comprise polymers comprising 99%, 98%, 97%, 96%, 95%, 90%, 85%, 80%, 75% or even less of biocompatible polymers, e.g., including polymers and other materials and excipients described herein, and still be biocompatible.

[0028] To determine whether a polymer or other material is biocompatible, it may be necessary to conduct a toxicity analysis. Such assays are well known in the art. One example of such an assay may be performed with live carcinoma cells, such as GT3TKB tumor cells, in the following manner: the sample is degraded in 1M NaOH at 37 °C until complete degradation is observed. The solution is then neutralized with 1M HCl. About 200 μL of various concentrations of the degraded sample products are placed in 96-well tissue culture plates and seeded with human gastric carcinoma cells (GT3TKB) at 104/well density. The degraded sample products are incubated with the GT3TKB cells for 48 hours. The results of the assay may be plotted as % relative growth vs. concentration of degraded sample in the tissue-culture well. In addition, polymers and formulations of the present invention may also be evaluated by well-known in vivo tests, such as subcutaneous implantations in rats to confirm that they do not cause significant levels of irritation or inflammation at the subcutaneous implantation sites.

[0029] The term "biodegradable" is art-recognized, and includes polymers, compositions and formulations, such as those described herein, that are intended to degrade during use. Biodegradable polymers typically differ from non-biodegradable polymers in that the former may be degraded during use. In certain embodiments, such use involves in vivo use, such as in vivo therapy, and in other certain embodiments, such use involves in vitro use. In general, degradation attributable to biodegradability involves the degradation of a biodegradable polymer into its component subunits, or digestion, e.g., by a biochemical process, of the polymer into smaller, non-polymeric subunits. In certain embodiments, two different types of biodegradation may generally be identified. For example, one type of biodegradation may involve cleavage of bonds (whether covalent or otherwise) in the polymer backbone. In such biodegradation, monomers and oligomers typically result, and even more typically, such biodegradation occurs by

cleavage of a bond connecting one or more of subunits of a polymer. In contrast, another type of biodegradation may involve cleavage of a bond (whether covalent or otherwise) internal to a side chain or that connects a side chain to the polymer backbone. In certain embodiments, one or the other or both generally types of biodegradation may occur during use of a polymer, and as used herein, the term "biodegradation" encompasses both general types of biodegradation.

[0030] The degradation rate of a biodegradable polymer often depends in part on a variety of factors, including the chemical identity of the linkage responsible for any degradation, the molecular weight, crystallinity, biostability, etc. of such polymer, the physical characteristics of the implant, shape and size, and the mode and location of administration. For example, the greater the molecular weight, the higher the degree of crystallinity, and/or the greater the biostability, the biodegradation of any biodegradable polymer is usually slower. The term "biodegradable" is intended to cover materials and processes also termed "bioerodible".

[0031] In certain embodiments, if the biodegradable polymer also has a therapeutic agent or other material associated with it, the biodegradation rate of such polymer may be characterized by a release rate of such materials. In such circumstances, the biodegradation rate may depend on not only the chemical identity and physical characteristics of the polymer, but also on the identity of any such material incorporated therein.

[0032] In certain embodiments, polymeric formulations of the present invention biodegrade within a period that is acceptable in the desired application. In certain embodiments, such as in vivo therapy, such degradation occurs in a period usually less than about five years, one year, six months, three months, one month, fifteen days, five days, three days, or even one day on exposure to a physiological solution with a pH between 6 and 8 having a temperature of between 25 and 37 °C. In other embodiments, the polymer degrades in a period of between about one hour and several weeks, depending on the desired application.

[0033] When used with respect to a therapeutic agent or other material, the term "sustained release" is art-recognized. For example, a subject composition which

releases a substance over time may exhibit sustained release characteristics, in contrast to a bolus type administration in which the entire amount of the substance is made biologically available at one time.

[0034] The term "delivery agent" is an art-recognized term, and includes molecules that facilitate the intracellular delivery of a therapeutic agent or other material. Examples of delivery agents include: sterols (e.g., cholesterol) and lipids (e.g., a cationic lipid, virosome or liposome).

[0035] The term "instructional material" or "instructions" includes a publication, a recording, a diagram, or any other medium of expression which can be used to communicate the usefulness of a subject composition described herein for a method of treatment or a method of making or using a subject composition. The instructional material may, for example, be affixed to a container which contains the composition or be shipped together with a container which contains the composition or be contained in a kit with the composition. Alternatively, the instructional material may be shipped separately from the container with the intention that the instructional material and the composition be used cooperatively by the recipient.

[0036] The term "microspheres" is art-recognized, and includes substantially spherical colloidal structures, e.g., formed from biocompatible polymers such as subject compositions, having a size ranging from about one or greater up to about 1000 microns. In general, "microcapsules", also an art-recognized term, may be distinguished from microspheres, because microcapsules are generally covered by a substance of some type, such as a polymeric formulation. The term "microparticles" is art-recognized, and includes microspheres and microcapsules, as well as structures that may not be readily placed into either of the above two categories, all with dimensions on average of less than 1000 microns. If the structures are less than about one micron in diameter, then the corresponding art-recognized terms "nanosphere," "nanocapsule," and "nanoparticle" may be utilized. In certain embodiments, the nanospheres, nancapsules and nanoparticles have an average diameter of about 500, 200, 100, 50 or 10 nm.

[0037] A composition comprising microspheres may include particles of a range of particle sizes. In certain embodiments, the particle size distribution may be uniform,

e.g., within less than about a 20% standard deviation of the median volume diameter, and in other embodiments, still more uniform or within about 10% of the median volume diameter.

[0038] The terms "number average molecular weight", or "Mn", "weight average molecular weight", "Z-average molecular weight" and "viscosity average molecular weight" are art-recognized. When the term "molecular weight" or an exemplary molecular weight is described herein, the measure of molecular weight will be clear from the context and/or will include all applicable measures.

[0039] The phrases "parenteral administration" and "administered parenterally" are art-recognized terms, and include modes of administration other than enteral and topical administration, such as injections, and include, without limitation, intravenous, intramuscular, intrapleural, intravascular, intrapericardial, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intra-articular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

[0040] The term "treating" is an art-recognized term which includes curing as well as ameliorating at least one symptom of any condition or disease.

[0041] The phrase "pharmaceutically acceptable" is art-recognized. In certain embodiments, the term includes compositions, polymers and other materials and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0042] The phrase "pharmaceutically acceptable carrier" is art-recognized, and includes, for example, pharmaceutically acceptable materials, compositions or vehicles, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting any subject composition from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of a subject composition and not injurious to the patient. In certain embodiments, a pharmaceutically acceptable carrier

is non-pyrogenic. Some examples of materials which may serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[0043] The term "pharmaceutically acceptable salts" is art-recognized, and includes relatively non-toxic, inorganic and organic acid addition salts of compositions of the present invention, including without limitation, therapeutic agents, excipients, other materials and the like. Examples of pharmaceutically acceptable salts include those derived from mineral acids, such as hydrochloric acid and sulfuric acid, and those derived from organic acids, such as ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like. Examples of suitable inorganic bases for the formation of salts include the hydroxides, carbonates, and bicarbonates of ammonia, sodium, lithium, potassium, calcium, magnesium, aluminum, zinc and the like. Salts may also be formed with suitable organic bases, including those that are non-toxic and strong enough to form such salts. For purposes of illustration, the class of such organic bases may include mono-, di-, and trialkylamines, such as methylamine, dimethylamine, and triethylamine; mono-, di- or trihydroxyalkylamines such as mono-, di-, and triethanolamine; amino acids, such as arginine and lysine; guanidine; N-methylglucosamine; N-methylglucamine; L-glutamine; N-methylpiperazine; morpholine; ethylenediamine; N-benzylphenethylamine; (trihydroxymethyl)aminoethane; and the like. See, for example, J. Pharm. Sci., 66:1-19 (1977).

[0044] A "patient," "subject," or "host" to be treated by the subject method may mean either a human or non-human animal, such as primates, mammals, and vertebrates.

[0045] The term "prophylactic or therapeutic" treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, i.e., it protects the host against developing the unwanted condition, whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

[0046] The term "preventing", when used in relation to a condition, such as cancer, an infectious disease, or other medical disease or condition, is well understood in the art, and includes administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a subject relative to a subject which does not receive the composition. Thus, prevention of cancer includes, for example, reducing the number of detectable cancerous growths in a population of patients receiving a prophylactic treatment relative to an untreated control population, and/or delaying the appearance of detectable cancerous growths in a treated population versus an untreated control population, e.g., by a statistically and/or clinically significant amount. Prevention of an infection includes, for example, reducing the number of diagnoses of the infection in a treated population versus an untreated control population, and/or delaying the onset of symptoms of the infection in a treated population versus an untreated control population.

[0047] The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" are art-recognized, and include the administration of a subject composition or other material other than directly into the central nervous system, e.g., by subcutaneous administration, such that it enters the patient's system and, thus, is subject to metabolism and other like processes.

[0048] The phrase "therapeutically effective amount" is an art-recognized term. In certain embodiments, the term refers to an amount of the therapeutic agent that, when incorporated into a polymer of the present invention, produces some desired effect at a reasonable benefit/risk ratio applicable to any medical treatment. In certain embodiments,

the term refers to that amount necessary or sufficient to eliminate, reduce or maintain (e.g., prevent the spread of) a tumor or other target of a particular therapeutic regimen. The effective amount may vary depending on such factors as the disease or condition being treated, the particular targeted constructs being administered, the size of the subject or the severity of the disease or condition. One of ordinary skill in the art may empirically determine the effective amount of a particular compound without necessitating undue experimentation.

[0049] In certain embodiments, a therapeutically effective amount of a biologically active agent, for in vivo use will likely depend on a number of factors, including: the rate of release of the agent from the a subject composition, which will depend in part on the chemical and physical characteristics of the polymer used; the identity of the agent; the mode and method of administration; and any other materials incorporated in the subject composition in addition to the biologically active agent.

[0050] The term "ED50" is art-recognized. In certain embodiments, ED50 means the dose of a drug which produces 50% of its maximum response or effect, or alternatively, the dose which produces a pre-determined response in 50% of test subjects or preparations. The term "LD50" is art-recognized. In certain embodiments, LD50 means the dose of a drug which is lethal in 50% of test subjects. The term "therapeutic index" is an art-recognized term which refers to the therapeutic index of a drug, defined as LD50/ED50.

[0051] The terms "incorporated" and "encapsulated" are art-recognized when used in reference to a therapeutic agent, or other material and a polymeric composition, such as a composition of the present invention. In certain embodiments, these terms include incorporating, formulating or otherwise including such agent into a composition which allows for sustained release of such agent in the desired application. The terms may contemplate any manner by which a therapeutic agent or other material is incorporated into a subject composition, including for example: attached to a monomer of such polymer (by covalent or other binding interaction) and having such monomer be part of the polymerization to give a polymeric formulation, distributed throughout the subject composition, appended to the surface of the subject composition (by covalent or

other binding interactions), encapsulated inside the subject composition, etc. The term "co-incorporation" or "co-encapsulation" refers to the incorporation of a therapeutic agent or other material and at least one other therapeutic agent or other material in a subject composition.

[0052] More specifically, the physical form in which any therapeutic agent or other material is encapsulated in polymers may vary with the particular embodiment. For example, a therapeutic agent or other material may be first encapsulated in a microsphere and then combined with the polymer in such a way that at least a portion of the microsphere structure is maintained. Alternatively, a therapeutic agent or other material may be sufficiently immiscible in the polymer of the invention that it is dispersed as small droplets, rather than being dissolved, in the polymer. Any form of encapsulation or incorporation is contemplated by the present invention, in so much as the sustained release of any encapsulated therapeutic agent or other material determines whether the form of encapsulation is sufficiently acceptable for any particular use.

[0053] The term "biocompatible plasticizer" is art-recognized, and includes materials which are soluble or dispersible in the compositions of the present invention, which increase the flexibility of a subject composition, and which, in the amounts employed, are biocompatible. Suitable plasticizers are well known in the art and include those disclosed in U.S. Patent Nos. 2,784,127 and 4,444,933. Specific plasticizers include, by way of example, acetyl tri-n-butyl citrate (c. 20 weight percent or less), acetyl trihexyl citrate (c. 20 weight percent or less), butyl benzyl phthalate, dibutyl phthalate, dioctylphthalate, n-butyryl tri-n-hexyl citrate, diethylene glycol dibenzoate (c. 20 weight percent or less) and the like.

[0054] "Small molecule" is an art-recognized term. In certain embodiments, this term refers to a molecule which has a molecular weight of less than about 2000 amu, or less than about 1000 amu, and even less than about 500 amu.

[0055] The term "aliphatic" is an art-recognized term and includes linear, branched, and cyclic alkanes, alkenes, or alkynes. In certain embodiments, aliphatic groups in the present invention are linear or branched and have from 1 to about 20 carbon atoms.

[0056] The term "alkyl" is art-recognized, and includes saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight chain or branched chain alkyl has about 30 or fewer carbon atoms in its backbone (e.g., C1-C30 for straight chain, C3-C30 for branched chain), and alternatively, about 20 or fewer. Likewise, cycloalkyls have from about 3 to about 10 carbon atoms in their ring structure, and alternatively about 5, 6 or 7 carbons in the ring structure. The term "alkyl" is also defined to include halosubstituted alkyls.

[0057] Moreover, the term "alkyl" (or "lower alkyl") includes "substituted alkyls", which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents may include, for example, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain may themselves be substituted, if appropriate. For instance, the substituents of a substituted alkyl may include substituted and unsubstituted forms of amino, azido, imino, amido, phosphoryl (including phosphonate and phosphinate), sulfonyl (including sulfate, sulfonamido, sulfamoyl and sulfonate), and silyl groups, as well as ethers, alkylthios, carbonyls (including ketones, aldehydes, carboxylates, and esters), -CN and the like. Exemplary substituted alkyls are described below. Cycloalkyls may be further substituted with alkyls, alkenyls, alkoxys, alkylthios, aminoalkyls, carbonyl-substituted alkyls, -CN, and the like.

[0058] The term "aralkyl" is art-recognized, and includes alkyl groups substituted with an aryl group (e.g., an aromatic or heteroaromatic group).

[0059] The terms "alkenyl" and "alkynyl" are art-recognized, and include unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively.

[0060] Unless the number of carbons is otherwise specified, "lower alkyl" refers to an alkyl group, as defined above, but having from one to ten carbons, alternatively from one to about six carbon atoms in its backbone structure. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths.

[0061] The term "heteroatom" is art-recognized, and includes an atom of any element other than carbon or hydrogen. Illustrative heteroatoms include boron, nitrogen, oxygen, phosphorus, sulfur and selenium, and alternatively oxygen, nitrogen or sulfur.

[0062] The term "aryl" is art-recognized, and includes 5-, 6- and 7-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles" or "heteroaromatics." The aromatic ring may be substituted at one or more ring positions with such substituents as described above, for example, halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, -CF3, -CN, or the like. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are "fused rings") wherein at least one of the rings is aromatic, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls.

[0063] The terms ortho, meta and para are art-recognized and apply to 1,2-, 1,3- and 1,4-disubstituted benzenes, respectively. For example, the names 1,2-dimethylbenzene and ortho-dimethylbenzene are synonymous.

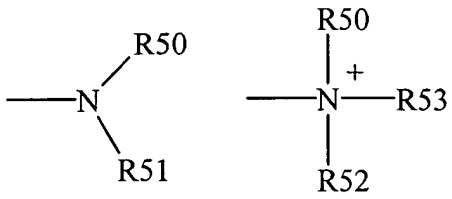
[0064] The terms "heterocyclyl" and "heterocyclic group" are art-recognized, and include 3- to about 10-membered ring structures, such as 3- to about 7-membered rings, whose ring structures include one to four heteroatoms. Heterocycles may also be polycycles. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole,

indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring may be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, -CF3, -CN, or the like.

[0065] The terms "polycyclyl" and "polycyclic group" are art-recognized, and include structures with two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Rings that are joined through non-adjacent atoms, e.g., three or more atoms are common to both rings, are termed "bridged" rings. Each of the rings of the polycycle may be substituted with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, -CF3, -CN, or the like.

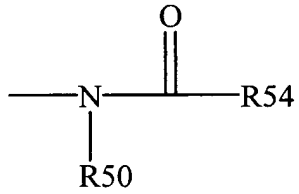
[0066] The term "carbocycle" is art recognized and includes an aromatic or non-aromatic ring in which each atom of the ring is carbon. The flowing art-recognized terms have the following meanings: "nitro" means -NO2; the term "halogen" designates -F, -Cl, -Br or -I; the term "sulfhydryl" means -SH; the term "hydroxyl" means -OH; and the term "sulfonyl" means -SO2-.

[0067] The terms "amine" and "amino" are art-recognized and include both unsubstituted and substituted amines, e.g., a moiety that may be represented by the general formulas:



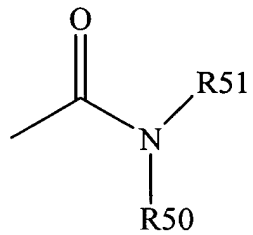
wherein R50, R51 and R52 each independently represent a hydrogen, an alkyl, an alkenyl, -(CH2)m-R61, or R50 and R51, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R61 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocycle or a polycycle; and m is zero or an integer in the range of 1 to 8. In certain embodiments, only one of R50 or R51 may be a carbonyl, e.g., R50, R51 and the nitrogen together do not form an imide. In other embodiments, R50 and R51 (and optionally R52) each independently represent a hydrogen, an alkyl, an alkenyl, or -(CH2)m-R61. Thus, the term "alkylamine" includes an amine group, as defined above, having a substituted or unsubstituted alkyl attached thereto, i.e., at least one of R50 and R51 is an alkyl group.

[0068] The term "acylamino" is art-recognized and includes a moiety that may be represented by the general formula:



wherein R50 is as defined above, and R54 represents a hydrogen, an alkyl, an alkenyl or -(CH2)m-R61, where m and R61 are as defined above.

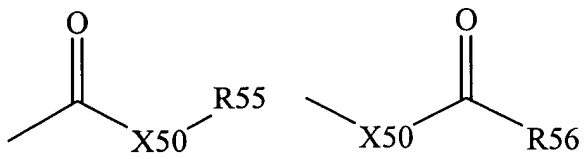
[0069] The term "amido" is art recognized as an amino-substituted carbonyl and includes a moiety that may be represented by the general formula:



wherein R50 and R51 are as defined above. Certain embodiments of the amide in the present invention will not include imides which may be unstable.

[0070] The term "alkylthio" is art recognized and includes an alkyl group, as defined above, having a sulfur radical attached thereto. In certain embodiments, the "alkylthio" moiety is represented by one of -S-alkyl, -S-alkenyl, -S-alkynyl, and -S-(CH2)m-R61, wherein m and R61 are defined above. Representative alkylthio groups include methylthio, ethyl thio, and the like.

[0071] The term "carbonyl" is art recognized and includes such moieties as may be represented by the general formulas:

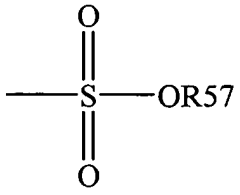


wherein X50 is a bond or represents an oxygen or a sulfur, and R55 represents a hydrogen, an alkyl, an alkenyl, -(CH2)m-R61or a pharmaceutically acceptable salt, R56 represents a hydrogen, an alkyl, an alkenyl or -(CH2)m-R61, where m and R61 are defined above. Where X50 is an oxygen and R55 or R56 is not hydrogen, the formula represents an "ester". Where X50 is an oxygen, and R55 is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R55 is a hydrogen, the formula represents a "carboxylic acid". Where X50 is an oxygen, and R56 is hydrogen, the formula represents a "formate". In general, where the oxygen atom of the above formula is replaced by sulfur, the formula represents a "thiocarbonyl" group. Where X50 is a sulfur and R55 or R56 is not hydrogen, the formula represents a "thioester." Where X50 is a sulfur and R55 is hydrogen, the formula represents a "thiocarboxylic acid." Where X50 is a sulfur and R56 is hydrogen, the formula represents a "thioformate." On the other hand, where X50 is a bond, and R55 is not hydrogen, the above formula represents a "ketone" group. Where X50 is a bond, and R55 is hydrogen, the above formula represents an "aldehyde" group.

[0072] The terms "alkoxyl" or "alkoxy" are art recognized and include an alkyl group, as defined above, having an oxygen radical attached thereto. Representative alkoxyl groups include methoxy, ethoxy, propyloxy, tert-butoxy and the like. An "ether"

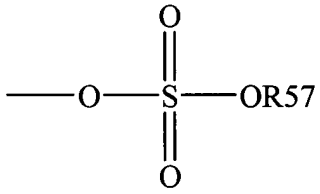
is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxyl, such as may be represented by one of -O-alkyl, -O-alkenyl, -O-alkynyl, -O-(CH2)m-R61, where m and R61 are described above.

[0073] The term "sulfonate" is art recognized and includes a moiety that may be represented by the general formula:



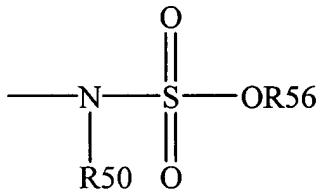
in which R57 is an electron pair, hydrogen, alkyl, cycloalkyl, or aryl.

[0074] The term "sulfate" is art recognized and includes a moiety that may be represented by the general formula:



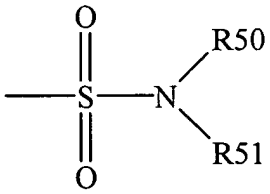
in which R57 is as defined above.

[0075] The term "sulfonamido" is art recognized and includes a moiety that may be represented by the general formula:



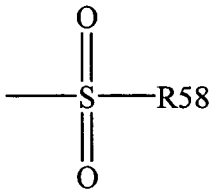
in which R50 and R56 are as defined above.

[0076] The term "sulfamoyl" is art-recognized and includes a moiety that may be represented by the general formula:



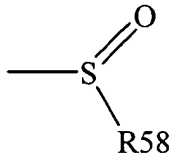
in which R50 and R51 are as defined above.

[0077] The term "sulfonyl" is art recognized and includes a moiety that may be represented by the general formula:



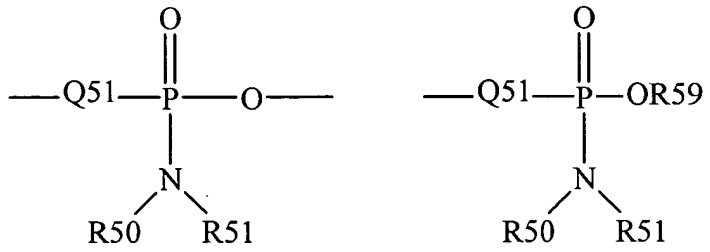
in which R58 is one of the following: hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl or heteroaryl.

[0078] The term "sulfoxido" is art recognized and includes a moiety that may be represented by the general formula:



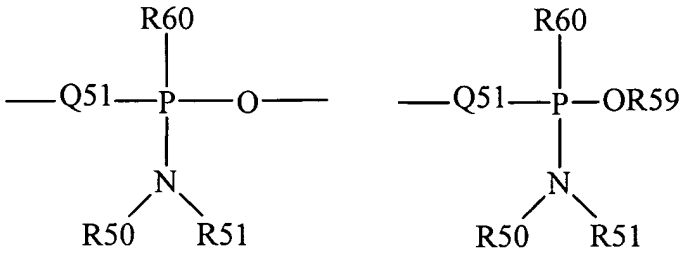
in which R58 is defined above.

[0079] The term "phosphoramidite" is art recognized and includes moieties represented by the general formulas:



wherein Q51, R50, R51 and R59 are as defined above.

[0080] The term "phosphonamidite" is art recognized and includes moieties represented by the general formulas:



wherein Q51, R50, R51 and R59 are as defined above, and R60 represents a lower alkyl or an aryl.

[0081] Analogous substitutions may be made to alkenyl and alkynyl groups to produce, for example, aminoalkenyls, aminoalkynyls, amidoalkenyls, amidoalkynyls, iminoalkenyls, iminoalkynyls, thioalkenyls, thioalkynyls, carbonyl-substituted alkenyls or alkynyls.

[0082] The definition of each expression, e.g. alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure unless otherwise indicated expressly or by the context.

[0083] The term "selenoalkyl" is art recognized and includes an alkyl group having a substituted seleno group attached thereto. Exemplary "selenoethers" which may be substituted on the alkyl are selected from one of -Se-alkyl, -Se-alkenyl, -Se-alkynyl, and -Se-(CH2)m-R61, m and R61 being defined above.

[0084] The terms triflyl, tosyl, mesyl, and nonaflyl are art-recognized and refer to trifluoromethanesulfonyl, p-toluenesulfonyl, methanesulfonyl, and nonafluorobutanesulfonyl groups, respectively. The terms triflate, tosylate, mesylate, and nonaflate are art-recognized and refer to trifluoromethanesulfonate ester, p-toluenesulfonate ester, methanesulfonate ester, and nonafluorobutanesulfonate ester functional groups and molecules that contain said groups, respectively.

[0085] The abbreviations Me, Et, Ph, Tf, Nf, Ts, and Ms are art recognized and represent methyl, ethyl, phenyl, trifluoromethanesulfonyl, nonafluorobutanesulfonyl, p-toluenesulfonyl and methanesulfonyl, respectively. A more comprehensive list of the

abbreviations utilized by organic chemists of ordinary skill in the art appears in the first issue of each volume of the Journal of Organic Chemistry; this list is typically presented in a table entitled Standard List of Abbreviations.

[0086] Certain monomeric subunits of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers and other compositions of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, R- and S-enantiomers, diastereomers, (d)-isomers, (l)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[0087] If, for instance, a particular enantiomer of a compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

[0088] It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction.

[0089] The term "substituted" is also contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents may be one or more

and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

[0090] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover. The term "hydrocarbon" is art recognized and includes all permissible compounds having at least one hydrogen and one carbon atom. For example, permissible hydrocarbons include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic organic compounds that may be substituted or unsubstituted.

[0091] The phrase "protecting group" is art recognized and includes temporary substituents that protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of protecting group chemistry has been reviewed. Greene et al., Protective Groups in Organic Synthesis 2nd ed., Wiley, New York, (1991).

[0092] The phrase "hydroxyl-protecting group" is art recognized and includes those groups intended to protect a hydroxyl group against undesirable reactions during synthetic procedures and includes, for example, benzyl or other suitable esters or ethers groups known in the art.

[0093] The term "electron-withdrawing group" is recognized in the art, and denotes the tendency of a substituent to attract valence electrons from neighboring atoms, i.e., the substituent is electronegative with respect to neighboring atoms. A quantification of the level of electron-withdrawing capability is given by the Hammett sigma (σ) constant. This well known constant is described in many references, for instance, March, Advanced Organic Chemistry 251-59, McGraw Hill Book Company, New York, (1977). The Hammett constant values are generally negative for electron donating groups (σ (P) = - 0.66 for NH2) and positive for electron withdrawing groups (σ (P) = 0.78 for a

nitro group), σ (P) indicating para substitution. Exemplary electron-withdrawing groups include nitro, acyl, formyl, sulfonyl, trifluoromethyl, cyano, chloride, and the like. Exemplary electron-donating groups include amino, methoxy, and the like.

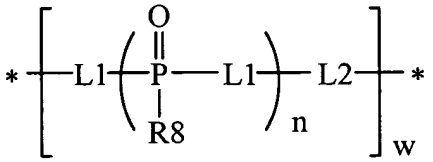
[0094] Contemplated equivalents of the polymers, subunits and other compositions described above include such materials which otherwise correspond thereto, and which have the same general properties thereof (e.g., biocompatible), wherein one or more simple variations of substituents are made which do not adversely affect the efficacy of such molecule to achieve its intended purpose. In general, the compounds of the present invention may be prepared by the methods illustrated in the general reaction schemes as, for example, described below, or by modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are in themselves known, but are not mentioned here.

3. Exemplary Subject Compositions

A. Polymers

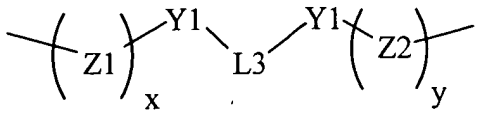
[0095] A variety of polymers may be used in the subject invention. Both non-biodegradable and biodegradable polymers may be used in the subject invention. For example, biodegradable polymers may be used. As discussed below, the choice of polymer will depend in part on a variety of physical and chemical characteristics of such polymer and the use to which such polymer may be put.

[0096] Monomeric units of certain of the subject polymers may be represented as follows

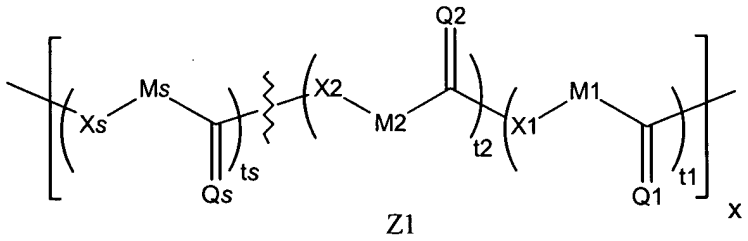


[0097] Formula I

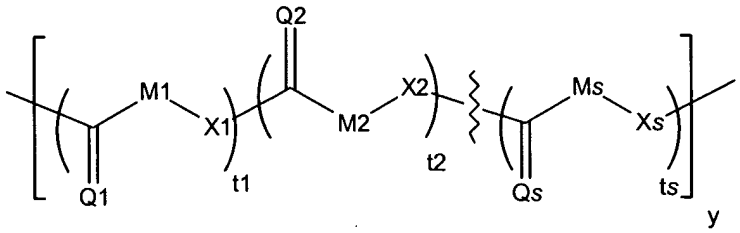
wherein, independently for each occurrence of said monomeric unit, L1 has the following formula:



[0098] wherein Z1 and Z2, respectively, for each independent occurrence is:



Z1



Z2

[0099] wherein, independently for each occurrence of said L1 unit:

[00100] Q1, Q2 ... Qs, each independently, represent -O- or -N(R7);

[00101] X1, X2 ... Xs, each independently, represent -O- or -N(R7);

[00102] M1, M2 ... Ms each independently, represents any chemical moiety that does not materially interfere with the biocompatibility of said polymer;

[00103] R7 represents -H, -aryl, -alkenyl or -alkyl;

[00104] the sum of t1, t2 ... ts is an integer and equal to at least one or more;

[00105] Y1 represents -O-, -S- or -N(R7)-;

[00106] x and y are each independently integers from 1 to about 1000 or more;

[00107] L3 represents any chemical moiety that does not materially interfere with the biocompatibility of said monomeric unit;

[00108] L2 represents a chemical moiety that does not materially interfere with the biocompatability of said monomeric unit and is terminated at each end with a -C(O)- radical;

[00109] R8 represents -H, alkyl, O-alkyl, cycloalkyl, O-cycloalkyl, cycloalkenyl, O-cycloalkenyl, aryl, O-aryl, heterocycle, O-heterocycle, polycycle, O-polycycle, or -N(R9)R10;

[00110] R9 and R10, each independently, represents -H, alkyl, alkenyl, -(CH2)m-R11, or R9 and R10, taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure;

[00111] R11 represents -H, alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycle or polycycle;

[00112] m represents an integer in the range of 0-10; and

[00113] n and w independently of each other represent an integer equal to at least one or more.

[00114] Such monomeric unit may be responsible in certain embodiments for biodegradability properties, if any, observed for a polymer containing such unit in vitro or in vivo.

[00115] In certain embodiments, R8 may represent an alkyl, aralkyl, alkoxy, alkylthio, or alkylamino group.

[00116] In Formula I and other formulas herein, "*" represents other monomeric units of the subject polymer, which may be the same or different from the unit depicted in the formula in question, or a chain terminating group, by which the polymer terminates. Examples of such chain terminating groups include monofunctional alcohols and amines.

[00117] In certain embodiments, the X1, X2...Xs moieties in such substructure are the same. For general guidance, when reference is made to the "polymer backbone chain" or the like of a polymer, with reference to the above structure, such polymer backbone chain comprises the motif [-L1-P-L1-L2]. In other polymers, the polymer backbone chain may vary as recognized by one of skill in the art.

[00118] L3 and L2 may be any chemical moiety as long as it does not materially interfere with the polymerization, biocompatibility or biodegradation (or any combination of those three properties) of the polymer, wherein a "material interference" or "non-interfering substituent" is understood to mean: (i) for synthesis of the polymer by

polymerization, an inability to prepare the subject polymer by methods known in the art or taught herein, (ii) for biocompatibility, a reduction in the biocompatibility of the subject polymer so as to make such polymer impracticable for in vivo use; and (iii) for biodegradation, a reduction in the biodegradation of the subject polymer so as to make such polymer impracticable for biodegradation.

[00119] In certain embodiments, L2 is an organic moiety, such as a divalent branched or straight chain or cyclic aliphatic group or divalent aryl group, with in certain embodiments, from 1 to about 20 carbon atoms and terminated at each end with a -(CO)- radical. In certain embodiments, L2 represents a moiety between about 2 and 20 atoms selected from carbon, oxygen, sulfur, and nitrogen, wherein at least 60% of the atoms are carbon. In certain embodiments, L2 may be an alkylene group, such as methylene, ethylene, 1,2-dimethylethylene, n-propylene, isopropylene, 2,2-dimethylpropylene, n-pentylene, n-hexylene, n-heptylene; an alkenylene group such as ethenylene, propenylene, 2-(3-propenyl)-dodecylene; and an alkynylene group such as ethynylene, proynylene, 1-(4-butynyl)-3-methyldecylene; and the like, wherein the alkylene group is terminated at each end with a -(CO)- radical.

[00120] Further, L2 may be a cycloaliphatic group, such as cyclopentylene, 2-methylcyclopentylene, cyclohexylene, cyclohexylenedimethylene, cyclohexenylene and the like. L2 may also be a divalent aryl group, such as phenylene, benzylene, naphthalene, phenanthrenylene and the like. Further, L2 may be a divalent heterocyclic group, such as pyrrolylene, furanylene, thiophenylene, alkylyene-pyrrolylene-alkylene, pyridinylene, pyrimidinylene and the like. In these embodiments the cycloaliphatic group, aryl group, and heterocyclic group are terminated at each end with a -(CO)- radical.

[00121] In an embodiment L2 is a -(CO)C6H4(CO)- diradical.

[00122] In certain embodiments, L3 is an organic moiety, such as a divalent branched or straight chain or cyclic aliphatic group or divalent aryl group, with in certain embodiments, from 1 to about 20 carbon atoms. In certain embodiments, L3 represents a moiety between about 2 and 20 atoms selected from carbon, oxygen, sulfur, and nitrogen, wherein at least 60% of the atoms are carbon. In certain embodiments, L3 may be an

alkylene group, such as methylene, ethylene, 1,2-dimethylethylene, n-propylene, isopropylene, 2,2-dimethylpropylene, n-pentylene, n-hexylene, n-heptylene; an alkenylene group such as ethenylene, propenylene, 2-(3-propenyl)-dodecylene; and an alkynylene group such as ethynylene, proynylene, 1-(4-butynyl)-3-methyldecylene; and the like.

[00123] Further, L3 may be a cycloaliphatic group, such as cyclopentylene, 2-methylcyclopentylene, cyclohexylene, cyclohexylenedimethylene, cyclohexenylene and the like. L3 may also be a divalent aryl group, such as phenylene, benzylene, naphthalene, phenanthrenylene and the like. Further, L3 may be a divalent heterocyclic group, such as pyrrolylene, furanylene, thiophenylene, alkylyene-pyrrolylene-alkylene, pyridinylene, pyrimidinylene and the like.

[00124] In an embodiment L3 is a -(CO)C6H4(CO)- diradical such that when Y1 is O, a terephthalate diradical is formed.

[00125] Other examples of L3 may include any polymer known to one of skill in the art, including, for example, polylactide, polyglycolide, polycaprolactone, polycarbonate, polyethylene terephthalate, polyanhydride and polyorthoester, and polymers of ethylene glycol, propylene glycol and the like. Embodiments containing such polymers for L3 may impart a variety of desired physical and chemical properties.

[00126] The foregoing, as with other moieties described herein, may be substituted with a non-interfering substituent, for example, a hydroxy-, halogen-, or nitrogen-substituted moiety.

[00127] The percentage of subunits L1 (or L3) to L2 may vary from less than 1:99 to more than 99:1, or alternatively 10:90, 15:85, 25:75, 40:60, 50:50, 60:40, 75:25, 85:15, 90:10 or the like.

[00128] R8 represents hydrogen, alkyl, cycloakyl, -O-alkyl, -O-cycloalkyl, aryl, -O-aryl, heterocycle, -O-heterocycle, or -N(R9)R10. Examples of possible alkyl R8 groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, tert-butyl, -C8H17 and the like groups; and alkyl substituted with a non-interfering substituent, such as hydroxy, halogen, alkoxy or nitro; corresponding alkoxy groups.

[00129] When R8 is aryl or the corresponding aryloxy group, it typically contains from about 5 to about 14 carbon atoms, or about 5 to about 12 carbon atoms, and optionally, may contain one or more rings that are fused to each other. Examples of particularly suitable aromatic groups include phenyl, phenoxy, naphthyl, anthracenyl, phenanthrenyl and the like.

[00130] When R8 is heterocyclic or heterocycloxy, it typically contains from about 5 to about 14 ring atoms, alternatively from about 5 to about 12 ring atoms, and one or more heteroatoms. Examples of suitable heterocyclic groups include furan, thiophene, pyrrole, isopyrrole, 3-isopyrrole, pyrazole, 2-isoimidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, thiazole, isothiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3,4-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-dioxazole, 1,2,4-dioxazole, 1,3,2-dioxazole, 1,3,4-dioxazole, 1,2,5-oxatriazole, 1,2-pyran, 1,4-pyran, 1,2-pyrone, 1,4-pyrone, 1,2-dioxin, 1,3-dioxin, pyridine, N-alkyl pyridinium, pyridazine, pyrimidine, pyrazine, 1,3,5-triazine, 1,2,4-triazine, 1,2,3-triazine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, o-isoxazine, p-isoxazine, 1,2,5-oxathiazine, 1,2,6-oxathiazine, 1,4,2-oxadiazine, 1,3,5-oxadiazine, azepine, oxepin, thiepin, indene, isoindene, benzofuran, isobenzofuran, thionaphthene, isothionaphthene, indole, indolenine, 2-isobenzazole, isoindazole, indoxazine, benzoxazole, anthranil, 1,2-benzopyran, 1,2-benzopyrone, 1,4-benzopyrone, 2,1-benzopyrone, 2,3-benzopyrone, quinoline, isoquinoline, 12, -benzodiazine, 1,3-benzodiazine, naphthyridine, pyrido-[3,4-b]-pyridine, pyrido-[3,2-b]-pyridine, pyrido-[4,3-b]-pyridine, 1,3,2-benzoxazine, 1,4,2-benzoxazine, 2,3,1-benzoxazine, 3,1,4-benzoxazine, 1,2-benzisoxazine, 1,4-benzisoxazine, carbazole, xanthrene, acridine, purine, and the like. In certain embodiments, when R8 is heterocyclic or heterocycloxy, it is selected from the group consisting of furan, pyridine, N-alkylpyridine, 1,2,3- and 1,2,4-triazoles, indene, anthracene and purine rings.

[00131] In certain embodiments, R8 is an alkyl group, an alkoxy group, a phenyl group, a phenoxy group, a heterocycloxy group, or an ethoxy group.

[00132] In still other embodiments, R8, such as an alkyl, may be conjugated to a bioactive substance to form a pendant drug delivery system.

[00133] M1, M2 ... Ms (collectively, M) in Formula I are each independently any chemical moiety that does not materially interfere with the polymerization, biocompatibility or biodegradation (or any combination of those three properties) of the subject compositions. For certain embodiments, M in the formula are each independently: (i) a branched or straight chain aliphatic or aryl group having from 1 to about 50 carbon atoms, or (ii) a branched or straight chain, oxa-, thia-, or aza-aliphatic group having from 1 to about 50 carbon atoms, both optionally substituted. In certain embodiments, the number of such carbon atoms does not exceed 20. In other embodiments, M may be any divalent aliphatic moiety having from 1 to about 20 carbon atoms, including therein from 1 to about 7 carbon atoms.

[00134] M may include an aromatic or heteroaromatic moiety, optionally with non-interfering substituents. In certain embodiments, none of the atoms (usually but not always C) that form the cyclic ring that gives rise to the aromatic moiety are part of the polymer backbone chain.

[00135] Specifically, when M is a branched or straight chain aliphatic group having from 1 to about 20 carbon atoms, it may be, for example, an alkylene group such as methylene, ethylene, 1-methylethylene, 1,2-dimethylethylene, n-propylene, trimethylene, isopropylene, 2,2-dimethylpropylene, n-pentylene, n-hexylene, n-heptylene, n-octylene, n-nonylene, n-decylene, n-undecylene, n-dodecylene, and the like; an alkenylene group such as n-propenylene, 2-vinylpropylene, n-butenylene, 3-thexylbutylene, n-pentenylene, 4-(3-propenyl)hexylene, n-octenylene, 1-(4-butenyl)-3-methyldecylene, 2-(3-propenyl)dodecylene, hexadecenylene and the like; an alkynylene group, such as ethynylene, propynylene, 3-(2-ethynyl)pentylene, n-hexynylene, 2-(2-propynyl)decylene, and the like; or any alkylene, alkenylene or alkynylene group, including those listed above, substituted with a materially non-interfering substituent, for example, a hydroxy, halogen or nitrogen group, such as 2-chloro-n-decylene, 1-hydroxy-3-ethenylbutylene, 2-propyl-6-nitro-10-dodecynylene, and the like. The moiety M may also include –(CH2)3-, -(CH2)5- and -(CH2)2OCH2-.

[00136] When M is a branched or straight chain oxaaliphatic group having from 1 to about 20 carbon atoms, it may be, for example, a divalent alkoxylene group, such as

ethoxylene, 2-methylethoxylene, propoxylene, butoxylene, pentoxylene, dodecyloxylene, hexadecyloxylene, and the like. When M is a branched or straight chain oxaaliphatic group, it may have the formula -(CH2)a-O-(CH2)b- wherein each of a and b, independently, is about 1 to about 7.

[00137] When M is a branched or straight chain oxaaliphatic group having from 1 to about 20 carbon atoms, it may also be, for example, a dioxaalkylene group such as dioxymethylene, dioxyethylene, 1,3-dioxypropylene, 2-methoxy-1,3-dioxypropylene, 1,3-dioxy-2-methylpropylene, dioxy-n-pentylene, dioxy-n-octadecylene, methoxylene-methoxylene, ethoxylene-methoxylene, ethoxylene-ethoxylene, ethoxylene-1-propoxylene, butoxylene-n-propoxylene, pentadecyloxylene-methoxylene, and the like. When M is a branched or straight chain, dioxyaliphatic group, it may have the formula -(CH2)a-O-(CH2)b-O-(CH2)c-, wherein each of a, b, and c is independently from 1 to about 7.

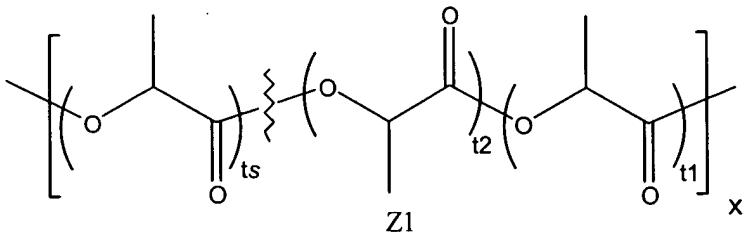
[00138] When M is a branched or straight chain thio-aliphatic group, the group may be any of the preceding oxaaliphatic groups wherein the oxygen atoms are replaced by sulfur atoms.

[00139] When M is a branched or straight chain, aza-aliphatic group having from 1 to about 20 carbon atoms, it may be a divalent group such as -CH2NH-, -(CH2)2N-, -CH2(C2H5)N-, -n-C4H9NH-, -t-C4H9NH-, -CH2(C3H7)N-, -C2H5(C2H5)N-, -CH2(C8H17)N-, -CH2NHCH2-, -(CH2)2NCH2-, -CH2(C2H5)NCH2CH2-, -n-C4H9NHCH2-, -t-C4H9NHCH2CH2-, -CH2(C3H7)N(CH2)4-, -C2H5(C2H5)NCH2-, -CH2(C8H17)NCH2CH2-,and the like. When M is a branched or straight chain, amino-aliphatic group, it may have the formula -(CH2)aNR1- or -(CH2)aN(R1)(CH2)b- where R1 is -H, aryl, alkenyl or alkyl and each of a and b is independently from about 1 to about 7.

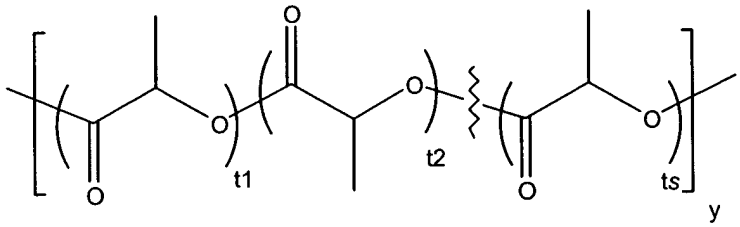
[00140] In certain embodiments, the number of monomeric units in Formula I and other subject formulas that make up the subject polymers ranges over a wide range, e.g., from about 5 to 25,000 or more, but generally from about 100 to 5000, or 10,000. Alternatively, in other embodiments, w may be about 10, 25, 50, 75, 100, 150, 200, 300 or 400.

[00141] The ratio of n:w which is the ratio of the phosphorous containing chains to the L2 linker may be anywhere from about 1:1 to 25,000:1, but generally from about 1:1 to about 1,000:1 or about 1:1 to about 100:1.

[00142] In certain embodiments, each of Z1 and Z2 in Formula I is represented by



Z1



Z2

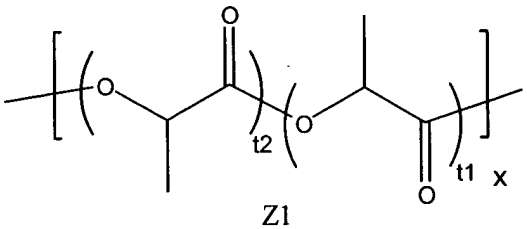
[00143] wherein, independently for each occurrence of Z1 and Z2:

[00144] the configuration of the chiral carbon for each ts may be D or L;

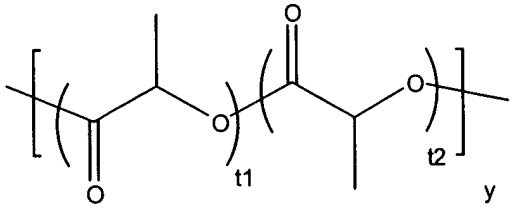
[00145] x and y are each independently integers from 1 to about 1000; and

[00146] the sum of t1, t2 ... ts is an integer and equal to at least one or more.

[00147] In a further embodiment each of Z1 and Z2 in Formula I is represented by



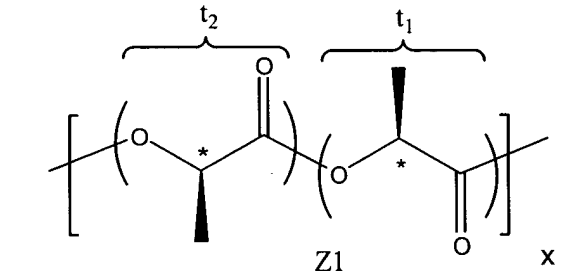
Z1



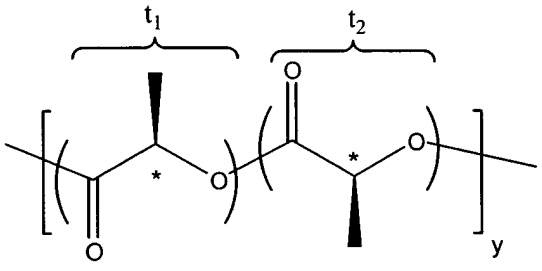
Z2

[00148] wherein, independently for each occurrence of Z1 and Z2, the configuration of the chiral carbons independently for each unit x for Z1 and unit y for Z2 is either D for t1 and L for t2, or L for t1 and D for t2. The variables x and y are each independently integers from 1 to about 1000.

[00149] Formula I (and all of the subject formulae and polymers) encompass a variety of different polymer structures, including block copolymers, random copolymers, random terpolymers and segmented block copolymers and terpolymers. Additional structures for Z of subject monomeric units are set forth below, which exemplify in part the variety of structures contemplated by the present invention:



Z1

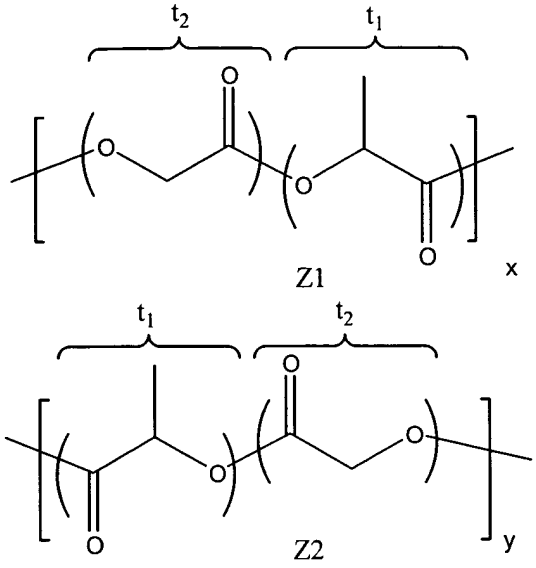


Z2

[00150] Formula Ia

[00151] Monomeric units and polymers that include the structure of Formula Ia (and other formulas described below), may also comprise further ts subunits depicted of the same molecular identity of those depicted in the formulas. For example, in Formula Ia, subunits t1 and t2 may be repeated in a sequence, e.g., alternating, in blocks (which may themselves repeat), or in any other pattern or random arrangement. Each subunit may repeat any number of times, and one subunit (e.g., t1) may occur with substantially the same frequency, more often, or less often than another subunit (e.g., t2), such that both subunits may be present in approximately the same amount, or in differing amounts, which may differ slightly or be highly disparate, e.g., one subunit is present nearly to the

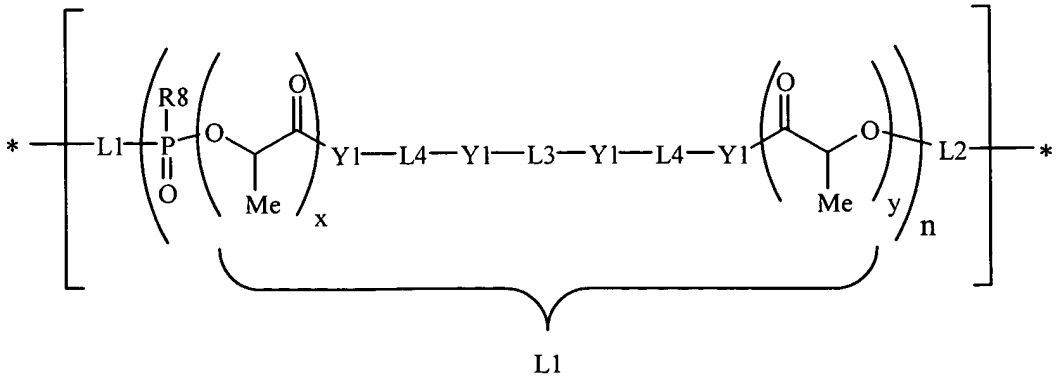
exclusion of the other. In certain embodiments, the chiral centers of each subunit may be the same or different and may be arranged in an orderly fashion or in a random sequence in each of Z1 and Z2.



[00152] Formula Ib

[00153] In certain embodiments of Formula Ib, the sum of the number of ts subunits in each of Z1 and Z2 is an even integer. As in other examples of Z1 and Z2, such as described above for Formula Ia, the ts subunits may be distributed randomly or in an ordered arrangement in each of Z1 or Z2.

[00154] In certain embodiments of Formula I, in which Q, M and X for each subunit are the same, Q1 represents O, M represents a lower alkylene group, and X1 represents O or N(R7). In an embodiment, X1 represents O. For example, M may represent -CH(CH3)- and L3 may be expanded upon to include a set of -L4-Y1- at either end to result in a polymer of Formula I having a structure represented in Formula II:



[00155] Formula II

wherein, independently for each occurrence set forth above:

[00156] L4 represents any chemical moiety that does not materially interfere with the biocompatibility of said polymer;

[00157] the other moieties are as defined above; and

[00158] x and y each independently represent integers in the range of about 1 to about 1000, e.g., about 1, about 10, about 20, about 50, about 100, about 250, about 500, about 750, about 1000, etc.

[00159] For Formula II, the average molar ratio of (x or y):L3, may vary greatly, typically between about 75:1 and about 2:1. In certain embodiments, the average molar ratio of (x or y):L3 is about 10:1 to about 2:1. The molar ratio of x:y may also vary; typically, such ratio is about 1. Other possible embodiments may have ratios of 0.1, 0.25, 0.5, 0.75, 1.5, 2, 3, 4, 10 and the like.

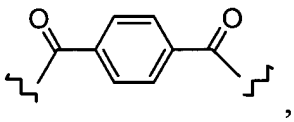
[00160] In certain embodiments, L4 is an organic moiety, such as a divalent branched or straight chain or cyclic aliphatic group or divalent aryl group, with in certain embodiments, from 1 to about 20 carbon atoms. In certain embodiments, L4 represents a moiety between about 2 and 20 atoms selected from carbon, oxygen, sulfur, and nitrogen, wherein at least 60% of the atoms are carbon. In certain embodiments, L4 may be an alkylene group, such as methylene, ethylene, 1,2-dimethylethylene, n-propylene, isopropylene, 2,2-dimethylpropylene, n-pentylene, n-hexylene, n-heptylene; an alkenylene group such as ethenylene, propenylene, 2-(3-propenyl)-dodecylene; and an alkynylene group such as ethynylene, proynylene, 1-(4-butynyl)-3-methyldecylene; and

the like. Such unsaturated aliphatic groups may be used to cross-link certain embodiments of the present invention.

[00161] Further, L4 may be a cycloaliphatic group, such as cyclopentylene, 2-methylcyclopentylene, cyclohexylene, cyclohexylenedimethylene, cyclohexenylene and the like. L4 may also be a divalent aryl group, such as phenylene, benzylene, naphthalene, phenanthrenylene and the like. Further, L4 may be a divalent heterocyclic group, such as pyrrolylene, furanylene, thiophenylene, alkylyene-pyrrolylene-alkylene, pyridinylene, pyrimidinylene and the like.

[00162] In certain embodiments, Y1 is -O-, L2 and L3 each represent a divalent aryl group, L4 represents a straight chain or branched aliphatic group, and R8 represents an alkyl group.

[00163] In a further embodiment, Y1 is -O-, L2 and L3 each represent a divalent aryl group of the formula:



where L4 is -CH2CH2-, and R8 is an ethyl group.

[00164] In certain embodiments of polymers depicted by Formula II, the chirality of each subunit is identical, whereas in other embodiments, the chirality is different. By way of example but not limitation, in Formula II above, if the chiral centers of all of the subunits are D-enantiomers or L-enantiomers, then the monomeric unit is effectively equivalent to D-lactic acid or L-lactic acid, respectively, thereby giving rise to a region similar to poly(D-lactic acid) or poly (L-lactic acid), respectively. Conversely, if the two subunits in Formula II are comprised of alternating D- and L-enantiomers (e.g., one unit of D-enantiomer, one unit of L-enantiomer, etc.), then the resulting polymeric region is analogous to poly(meso-lactic acid) (i.e., a polymer formed by polymerization of meso-lactide).

[00165] Finally, in certain embodiments of the monomeric units set forth in Formula I, in which the entire polymer may or may not be composed of such units, the

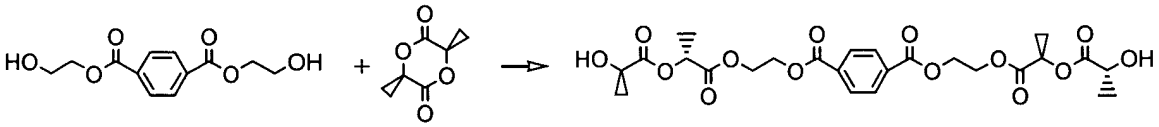
following moieties for Y1, L1, and R8 are possible. Further, a variety of different x and y are possible for a given moiety.

[00166]

Abbreviation	**All Y1's**	**L1**	**L2**	**R8**
P(DABHET-EOP/TC)	O	DABHET*	TC**	-OCH2CH3
P(DABHET-HOP/TC)	O	DABHET	TC	-O(CH2)5CH3
P(DLABHET-HOP/TC)	O	DLABHET	TC	-OCH2CH3
P(LABHET-EOP/TC)	O	LABHET	TC	-OCH2CH3
P(LABHET-HOP/TC)	O	LABHET	TC	-O(CH2)5CH3

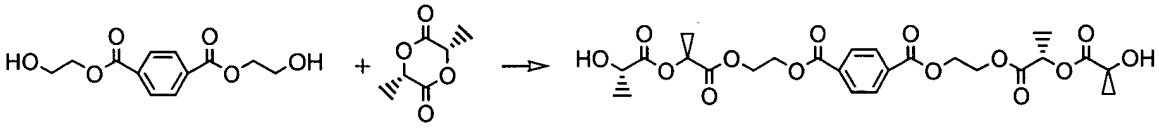
* DABHET is comprised of D-lactide (DA) and Bis(2-hydroxyethyl) terephthalate (BHET) in a 2 to 1 ratio (DA:BHET=2:1). Similarly, LABHET is comprised of L-lactide and BHET in a 2:1 ratio. DLABHET is comprised of D,L-lactide and BHET in a 2:1 ratio. See below.

**TC is terephthaloyl chloride. See below.



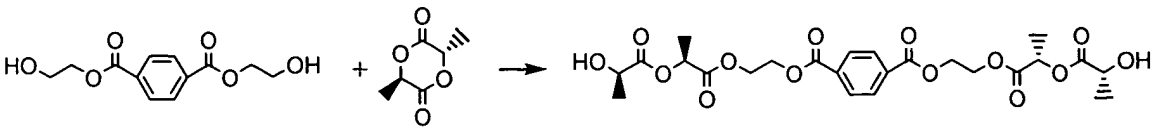
BHET + DA → DABHET prepolymer

1 : 2 DA:BHET = 2:1



BHET + LA → LABHET prepolymer

1 : 2 LA:BHET = 2:1



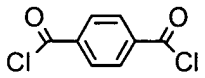
BHET : D,LA

1 : 2

D,LABHET prepolymer

D,LA:BHET = 2:1

1 of 4 stereoisomers



terephthaloyl chloride

[00167] In addition to the particular chiral version of the subject polymers described in the above table, polymers in which the chirality of MS varies in each subunit M in the subject polymers are also possible. For instance, referring to DLABHET(EOP)TC by example, a random order of D and L, in varying amounts, are possible for this polymer. In contrast, the table sets forth one such example in which a D and L chiral M are always adjacent, in equal amounts, but that need not always be the case.

[00168] The properties of the biocompatible polymers that make up the compositions of the present invention can be adjusted by varying the amounts and the nature of L2 to L1. For example, Figures 1-3 show molecular weight loss and glass temperature of degrading biocompatible polymers as compared to a polymer according to Formula I with and without the L2 linker. In these exemplary embodiments, L2 is terephthalate. Figure 1 shows that the molecular weight drop off for the degrading biocompatible polymers is rapid at first, when L2 is present, and then proceeds at the same rate as when L2 is absent. These results suggest that the amount of degradation as measured by molecular weight loss can be varied greatly especially within the first 10 days by the amount of L2 present relative to L1. An increase in the number of ring structures, for example, aryl moities, in the backbone of a polymer may result in higher glass temperatures. For example, Figure 3 shows that the glass temperature increases by about 10 °C when terephthalate is present, as compared to when it is absent.

[00169] In certain embodiments, the polymers are comprised almost entirely, if not entirely, of the same subunit. Alternatively, in other embodiments, the polymers may be copolymers, in which different subunits and/or other monomeric units are incorporated into the polymer. In certain instances, the polymers are random copolymers, in which the different subunits and/or other monomeric units are distributed randomly throughout the polymer chain. For example, the polymer having units of Formula II may consist of effectively only one type of such subunit, or alternatively two or more types of such subunits. In addition, the polymer may contain monomeric units other than those subunits represented by Formula II.

[00170] In other embodiments, the different types of monomeric units, be they one or more subunits depicted by the subject formulas or other monomeric units, are distributed randomly throughout the chain. In part, the term "random" is intended to refer to the situation in which the particular distribution or incorporation of monomeric units in a polymer that has more than one type of monomeric units is not directed or controlled directly by the synthetic protocol, but instead results from features inherent to the polymer system, such as the reactivity, amounts of subunits and other characteristics of the synthetic reaction or other methods of manufacture, processing or treatment.

[00171] Monomeric units that generally have the same structure may be bonded together in a polymer chain. For example, 2 to about 20 monomeric units of the same chemical moiety or structure may be bonded together in the polymer chain. This type of chain uniformity may be achieved, for example, by controlled synthesis of the prepolymer between one kind of bifunctional initiator and cyclic compound in a fixed ratio. A subsequent two step reaction with the same phosphorous containing compound and L2 linker may then be used.

[00172] In certain embodiments, the polymeric chains of the subject compositions, e.g., which include repetitive elements shown in any of the subject formulas, have molecular weights ranging from about 2000 or less to about 1,000,000 or more daltons, more particularly at least about 10,000 daltons, and even more specifically at least about 25,000 daltons or even at least 50,000 daltons. Number-average molecular weight (Mn) may also vary widely, but generally fall in the range of about 1,000 to about 400,000

daltons, about 1,000 to about 100,000 daltons and, in some embodiments, from about 1,000 to about 70,000 daltons. Mn, may, in some embodiments, vary between about 8,000 and 50,000 daltons.

[00173] One method to determine molecular weight is by gel permeation chromatography ("GPC"), e.g., mixed bed columns, CH2Cl2 solvent, and a refractive index detector (RI detector). Other methods are known in the art.

[00174] The glass transition temperature (Tg) of the subject polymers may vary widely, and depend on a variety of factors, such as the ratio between lactide and BHET components, the Mw of the final polymer, and the like. The Tg of the polymers is often within the range of from about 0 °C to about 80 °C, particularly between about 10 °C and 60 °C and, even more particularly between about 20 °C to about 50 °C.

[00175] In other embodiments, the polymer composition of the invention may be a flexible or flowable material. By "flowable" is meant the ability to assume, over time, the shape of the space containing it at body temperature. This includes, for example, liquid compositions that are capable of being sprayed into a site; injected with a manually operated syringe fitted with, for example, a 23-gauge needle; or delivered through a catheter.

[00176] Also included by the term "flowable", are highly viscous, "gel-like" materials at room temperature that may be delivered to the desired site by pouring, squeezing from a tube, or being injected with any one of the commercially available power injection devices that provide injection pressures greater than would be exerted by manual means alone for highly viscous, but still flowable, materials. When the polymer used is itself flowable, the polymer composition of the invention, even when viscous, need not include a biocompatible solvent to be flowable, although trace or residual amounts of biocompatible solvents may still be present.

[00177] In certain embodiments, the subject polymers are soluble in one or more common organic solvents for ease of fabrication and processing. Common organic solvents include such solvents as chloroform, dichloromethane, dichloroethane, 2-butanone, butyl acetate, ethyl butyrate, acetone, ethyl acetate, dimethylacetamide, N-methyl pyrrolidone, dimethylformamide, and dimethylsulfoxide.

B. Therapeutic compositions

[00178] In one aspect of this invention, a composition comprising a subject polymer and one or more therapeutic agents may be prepared. The therapeutic agent may vary widely with the intended purpose for the composition. The term "therapeutic agent" is art-recognized and refers to any chemical moiety that is a biologically, physiologically, or pharmacologically active substance that act locally or systemically in a subject. Examples of therapeutic agents, also referred to as "drugs", are described in well-known literature references such as the Merck Index, the Physicians Desk Reference, and The Pharmacological Basis of Therapeutics, and they include, without limitation, medicaments; vitamins; mineral supplements; substances used for the treatment, prevention, diagnosis, cure or mitigation of a disease or illness; substances which affect the structure or function of the body; or pro-drugs, which become biologically active or more active after they have been placed in a physiological environment. Various forms of a therapeutic agent may be used which are capable of being released from the subject composition into adjacent tissues or fluids upon administration to a subject.

[00179] In certain embodiments, the subject compositions comprise about 1% to about 80% or more by weight of the total composition, alternatively about 10%, 20%, 30%, 40%, 50%, 60% or 70%, of a therapeutic agent.

[00180] Non-limiting examples of therapeutic agents include the following: adrenergic blocking agents, anabolic agents, androgenic steroids, antacids, anti-asthmatic agents, anti-allergenic materials, anti-cholesterolemic and anti-lipid agents, anti-cholinergics and sympathomimetics, anti-coagulants, anti-convulsants, anti-diarrheals, anti-emetics, anti-hypertensive agents, anti-infective agents, anti-inflammatory agents such as steroids, non-steroidal anti-inflammatory agents, anti-malarials, anti-manic agents, anti-nauseants, anti-neoplastic agents, anti-obesity agents, anti-parkinsonian agents, anti-pyretic and analgesic agents, anti-spasmodic agents, anti-thrombotic agents, anti-uricemic agents, anti-anginal agents, antihistamines, anti-tussives, appetite suppressants, benzophenanthridine alkaloids, biologicals, cardioactive agents, cerebral dilators, coronary dilators, decongestants, diuretics, diagnostic agents, erythropoietic agents, estrogens, expectorants, gastrointestinal sedatives, humoral agents, hyperglycemic

agents, hypnotics, hypoglycemic agents, ion exchange resins, laxatives, mineral supplements, miotics, mucolytic agents, neuromuscular drugs, nutritional substances, peripheral vasodilators, progestational agents, prostaglandins, psychic energizers, psychotropics, sedatives, stimulants, thyroid and anti-thyroid agents, tranquilizers, uterine relaxants, vitamins, antigenic materials, and pro-drugs.

[00181] Specific examples of useful therapeutic agents from the above categories include: (a) anti-neoplastics such as androgen inhibitors, antimetabolites, cytotoxic agents, and immunomodulators; (b) anti-tussives such as dextromethorphan, dextromethorphan hydrobromide, noscapine, carbetapentane citrate, and chlophedianol hydrochloride; (c) antihistamines such as chlorpheniramine maleate, phenindamine tartrate, pyrilamine maleate, doxylamine succinate, and phenyltoloxamine citrate; (d) decongestants such as phenylephrine hydrochloride, phenylpropanolamine hydrochloride, pseudoephedrine hydrochloride, and ephedrine; (e) various alkaloids such as codeine phosphate, codeine sulfate, and morphine; (f) mineral supplements such as potassium chloride, zinc chloride, calcium carbonate, magnesium oxide, and other alkali metal and alkaline earth metal salts; (g) ion exchange resins such as cholestyramine; (h) anti-arrhythmics such as N-acetylprocainamide; (i) antipyretics and analgesics such as acetaminophen, aspirin and ibuprofen; (j) appetite suppressants such as phenyl-propanolamine hydrochloride or caffeine; (k) expectorants such as guaifenesin; (l) antacids such as aluminum hydroxide and magnesium hydroxide; (m) biologicals such as peptides, polypeptides, proteins and amino acids, hormones, interferons or cytokines and other bioactive peptidic compounds, such as hGH, tPA, calcitonin, ANF, EPO and insulin; (n) anti-infective agents such as anti-fungals, anti-virals, antiseptics and antibiotics; and (m) desensitizing agents and antigenic materials, such as those useful for vaccine applications.

[00182] More specifically, non-limiting examples of useful therapeutic agents include the following therapeutic categories: analgesics, such as nonsteroidal anti-inflammatory drugs, opiate agonists and salicylates; antihistamines, such as H1-blockers and H2-blockers; anti-infective agents, such as antihelmintics, antianaerobics, antibiotics, aminoglycoside antibiotics, antifungal antibiotics, cephalosporin antibiotics, macrolide antibiotics, miscellaneous ß-lactam antibiotics, penicillin antibiotics, quinolone

antibiotics, sulfonamide antibiotics, tetracycline antibiotics, antimycobacterials, antituberculosis antimycobacterials, antiprotozoals, antimalarial antiprotozoals, antiviral agents, anti-retroviral agents, scabicides, and urinary anti-infectives; antineoplastic agents, such as alkylating agents, nitrogen mustard alkylating agents, nitrosourea alkylating agents, antimetabolites, purine analog antimetabolites, pyrimidine analog antimetabolites, hormonal antineoplastics, natural antineoplastics, antibiotic natural antineoplastics, and vinca alkaloid natural antineoplastics; autonomic agents, such as anticholinergics, antimuscarinic anticholinergics, ergot alkaloids, parasympathomimetics, cholinergic agonist parasympathomimetics, cholinesterase inhibitor parasympathomimetics, sympatholytics, α-blocker sympatholytics, ß-blocker sympatholytics, sympathomimetics, and adrenergic agonist sympathomimetics; cardiovascular agents, such as antianginals, ß-blocker antianginals, calcium-channel blocker antianginals, nitrate antianginals, antiarrhythmics, cardiac glycoside antiarrhythmics, class I antiarrhythmics, class II antiarrhythmics, class III antiarrhythmics, class IV antiarrhythmics, antihypertensive agents, α-blocker antihypertensives, angiotensin-converting enzyme inhibitor (ACE inhibitor) antihypertensives, ß-blocker antihypertensives, calcium-channel blocker antihypertensives, central-acting adrenergic antihypertensives, diuretic antihypertensive agents, peripheral vasodilator antihypertensives, antilipemics, bile acid sequestrant antilipemics, HMG-CoA reductase inhibitor antilipemics, inotropes, cardiac glycoside inotropes, and thrombolytic agents; dermatological agents, such as antihistamines, anti-inflammatory agents, corticosteroid anti-inflammatory agents, antipruritics/local anesthetics, topical anti-infectives, antifungal topical anti-infectives, antiviral topical anti-infectives, and topical antineoplastics; electrolytic and renal agents, such as acidifying agents, alkalinizing agents, diuretics, carbonic anhydrase inhibitor diuretics, loop diuretics, osmotic diuretics, potassium-sparing diuretics, thiazide diuretics, electrolyte replacements, and uricosuric agents; enzymes, such as pancreatic enzymes and thrombolytic enzymes; gastrointestinal agents, such as antidiarrheals, antiemetics, gastrointestinal anti-inflammatory agents, salicylate gastrointestinal anti-inflammatory agents, antacid anti-ulcer agents, gastric acid-pump inhibitor anti-ulcer agents, gastric mucosal anti-ulcer agents, H2-blocker anti-ulcer agents, cholelitholytic agents, digestants,

emetics, laxatives and stool softeners, and prokinetic agents; general anesthetics, such as inhalation anesthetics, halogenated inhalation anesthetics, intravenous anesthetics, barbiturate intravenous anesthetics, benzodiazepine intravenous anesthetics, and opiate agonist intravenous anesthetics; hematological agents, such as antianemia agents, hematopoietic antianemia agents, coagulation agents, anticoagulants, hemostatic coagulation agents, platelet inhibitor coagulation agents, thrombolytic enzyme coagulation agents, and plasma volume expanders; hormones and hormone modifiers, such as abortifacients, adrenal agents, corticosteroid adrenal agents, androgens, anti-androgens, antidiabetic agents, sulfonylurea antidiabetic agents, antihypoglycemic agents, oral contraceptives, progestin contraceptives, estrogens, fertility agents, oxytocics, parathyroid agents, pituitary hormones, progestins, antithyroid agents, thyroid hormones, and tocolytics; immunobiologic agents, such as immunoglobulins, immunosuppressives, toxoids, and vaccines; local anesthetics, such as amide local anesthetics and ester local anesthetics; musculoskeletal agents, such as anti-gout anti-inflammatory agents, corticosteroid anti-inflammatory agents, gold compound anti-inflammatory agents, immunosuppressive anti-inflammatory agents, nonsteroidal anti-inflammatory drugs (NSAIDs), salicylate anti-inflammatory agents, skeletal muscle relaxants, neuromuscular blocker skeletal muscle relaxants, and reverse neuromuscular blocker skeletal muscle relaxants; neurological agents, such as anticonvulsants, barbiturate anticonvulsants, benzodiazepine anticonvulsants, anti-migraine agents, anti-parkinsonian agents, anti-vertigo agents, opiate agonists, and opiate antagonists; ophthalmic agents, such as anti-glaucoma agents, ß-blocker anti-glaucoma agents, miotic anti-glaucoma agents, mydriatics, adrenergic agonist mydriatics, antimuscarinic mydriatics, ophthalmic anesthetics, ophthalmic anti-infectives, ophthalmic aminoglycoside anti-infectives, ophthalmic macrolide anti-infectives, ophthalmic quinolone anti-infectives, ophthalmic sulfonamide anti-infectives, ophthalmic tetracycline anti-infectives, ophthalmic anti-inflammatory agents, ophthalmic corticosteroid anti-inflammatory agents, and ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs); psychotropic agents, such as antidepressants, heterocyclic antidepressants, monoamine oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants, antimanics, antipsychotics, phenothiazine

antipsychotics, anxiolytics, sedatives, and hypnotics, barbiturate sedatives and hypnotics, benzodiazepine anxiolytics, sedatives, and hypnotics, and psychostimulants; respiratory agents, such as antitussives, bronchodilators, adrenergic agonist bronchodilators, antimuscarinic bronchodilators, expectorants, mucolytic agents, respiratory anti-inflammatory agents, and respiratory corticosteroid anti-inflammatory agents; toxicology agents, such as antidotes, heavy metal antagonists/chelating agents, substance abuse agents, deterrent substance abuse agents, and withdrawal substance abuse agents; minerals; and vitamins, such as vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, and vitamin K.

[00183] Other classes of therapeutic agents from the above categories include: (1) analgesics in general, such as lidocaine, other caine analgesics or derivatives thereof, and nonsteroidal anti-inflammatory drugs (NSAIDs) analgesics, including diclofenac, ibuprofen, ketoprofen, and naproxen; (2) opiate agonist analgesics, such as codeine, fentanyl, hydromorphone, and morphine; (3) salicylate analgesics, such as aspirin (ASA) (enteric coated ASA); (4) H1-blocker antihistamines, such as clemastine and terfenadine; (5) H2-blocker antihistamines, such as cimetidine, famotidine, nizadine, and ranitidine; (6) anti-infective agents, such as mupirocin; (7) antianaerobic anti-infectives, such as chloramphenicol and clindamycin; (8) antifungal antibiotic anti-infectives, such as amphotericin b, clotrimazole, fluconazole, and ketoconazole; (9) macrolide antibiotic anti-infectives, such as azithromycin and erythromycin; (10) miscellaneous ß-lactam antibiotic anti-infectives, such as aztreonam and imipenem; (11) penicillin antibiotic anti-infectives, such as nafcillin, oxacillin, penicillin G, and penicillin V; (12) quinolone antibiotic anti-infectives, such as ciprofloxacin and norfloxacin; (13) tetracycline antibiotic anti-infectives, such as doxycycline, minocycline, and tetracycline; (14) antituberculosis antimycobacterial anti-infectives such as isoniazid (INH), and rifampin; (15) antiprotozoal anti-infectives, such as atovaquone and dapsone; (16) antimalarial antiprotozoal anti-infectives, such as chloroquine and pyrimethamine; (17) anti-retroviral anti-infectives, such as ritonavir and zidovudine; (18) antiviral anti-infective agents, such as acyclovir, ganciclovir, interferon alfa, and rimantadine; (19) alkylating antineoplastic agents, such as carboplatin and cisplatin; (20) nitrosourea alkylating antineoplastic agents, such as carmustine (BCNU); (21) antimetabolite antineoplastic agents, such as

methotrexate; (22) pyrimidine analog antimetabolite antineoplastic agents, such as fluorouracil (5-FU) and gemcitabine; (23) hormonal antineoplastics, such as goserelin, leuprolide, and tamoxifen; (24) natural antineoplastics, such as aldesleukin, interleukin-2, docetaxel, etoposide (VP-16), interferon alfa, paclitaxel, other taxane derivatives, and tretinoin (ATRA); (25) antibiotic natural antineoplastics, such as bleomycin, dactinomycin, daunorubicin, doxorubicin, and mitomycin; (26) vinca alkaloid natural antineoplastics, such as vinblastine and vincristine; (27) autonomic agents, such as nicotine; (28) anticholinergic autonomic agents, such as benztropine and trihexyphenidyl; (29) antimuscarinic anticholinergic autonomic agents, such as atropine and oxybutynin; (30) ergot alkaloid autonomic agents, such as bromocriptine; (31) cholinergic agonist parasympathomimetics, such as pilocarpine; (32) cholinesterase inhibitor parasympathomimetics, such as pyridostigmine; (33) α-blocker sympatholytics, such as prazosin; (34) ß-blocker sympatholytics, such as atenolol; (35) adrenergic agonist sympathomimetics, such as albuterol and dobutamine; (36) cardiovascular agents, such as aspirin (ASA) (enteric coated ASA); (37) ß-blocker antianginals, such as atenolol and propranolol; (38) calcium-channel blocker antianginals, such as nifedipine and verapamil; (39) nitrate antianginals, such as isosorbide dinitrate (ISDN); (40) cardiac glycoside antiarrhythmics, such as digoxin; (41) class I antiarrhythmics, such as lidocaine, mexiletine, phenytoin, procainamide, and quinidine; (42) class II antiarrhythmics, such as atenolol, metoprolol, propranolol, and timolol; (43) class III antiarrhythmics, such as amiodarone; (44) class IV antiarrhythmics, such as diltiazem and verapamil; (45) β-blocker antihypertensives, such as prazosin; (46) angiotensin-converting enzyme inhibitor (ACE inhibitor) antihypertensives, such as captopril and enalapril; (47) ß-blocker antihypertensives, such as atenolol, metoprolol, nadolol, and propanolol; (48) calcium-channel blocker antihypertensive agents, such as diltiazem and nifedipine; (49) central-acting adrenergic antihypertensives, such as clonidine and methyldopa; (50) diurectic antihypertensive agents, such as amiloride, furosemide, hydrochlorothiazide (HCTZ), and spironolactone; (51) peripheral vasodilator antihypertensives, such as hydralazine and minoxidil; (52) antilipemics, such as gemfibrozil and probucol; (53) bile acid sequestrant antilipemics, such as cholestyramine; (54) HMG-CoA reductase inhibitor antilipemics, such as lovastatin and pravastatin; (55) inotropes, such as

amrinone, dobutamine, and dopamine; (56) cardiac glycoside inotropes, such as digoxin; (57) thrombolytic agents, such as alteplase (TPA), anistreplase, streptokinase, and urokinase; (58) dermatological agents, such as colchicine, isotretinoin, methotrexate, minoxidil, tretinoin (ATRA); (59) dermatological corticosteroid anti-inflammatory agents, such as betamethasone and dexamethasone; (60) antifungal topical anti-infectives, such as amphotericin B, clotrimazole, miconazole, and nystatin; (61) antiviral topical anti-infectives, such as acyclovir; (62) topical antineoplastics, such as fluorouracil (5-FU); (63) electrolytic and renal agents, such as lactulose; (64) loop diuretics, such as furosemide; (65) potassium-sparing diuretics, such as triamterene; (66) thiazide diuretics, such as hydrochlorothiazide (HCTZ); (67) uricosuric agents, such as probenecid; (68) enzymes such as RNase and DNase; (69) thrombolytic enzymes, such as alteplase, anistreplase, streptokinase and urokinase; (70) antiemetics, such as prochlorperazine; (71) salicylate gastrointestinal anti-inflammatory agents, such as sulfasalazine; (72) gastric acid-pump inhibitor anti-ulcer agents, such as omeprazole; (73) H2-blocker anti-ulcer agents, such as cimetidine, famotidine, nizatidine, and ranitidine; (74) digestants, such as pancrelipase; (75) prokinetic agents, such as erythromycin; (76) opiate agonist intravenous anesthetics such as fentanyl; (77) hematopoietic antianemia agents, such as erythropoietin, filgrastim (G-CSF), and sargramostim (GM-CSF); (78) coagulation agents, such as antihemophilic factors 1-10 (AHF 1-10); (79) anticoagulants, such as warfarin; (80) thrombolytic enzyme coagulation agents, such as alteplase, anistreplase, streptokinase and urokinase; (81) hormones and hormone modifiers, such as bromocriptine; (82) abortifacients, such as methotrexate; (83) antidiabetic agents, such as insulin; (84) oral contraceptives, such as estrogen and progestin; (85) progestin contraceptives, such as levonorgestrel and norgestrel; (86) estrogens such as conjugated estrogens, diethylstilbestrol (DES), estrogen (estradiol, estrone, and estropipate); (87) fertility agents, such as clomiphene, human chorionic gonadotropin (HCG), and menotropins; (88) parathyroid agents such as calcitonin; (89) pituitary hormones, such as desmopressin, goserelin, oxytocin, and vasopressin (ADH); (90) progestins, such as medroxyprogesterone, norethindrone, and progesterone; (91) thyroid hormones, such as levothyroxine; (92) immunobiologic agents, such as interferon beta-1b and interferon gamma-1b; (93) immunoglobulins, such as immune globulin IM, IMIG, IGIM and

immune globulin IV, IVIG, IGIV; (94) amide local anesthetics, such as lidocaine; (95) ester local anesthetics, such as benzocaine and procaine; (96) musculoskeletal corticosteroid anti-inflammatory agents, such as beclomethasone, betamethasone, cortisone, dexamethasone, hydrocortisone, and prednisone; (97) musculoskeletal anti-inflammatory immunosuppressives, such as azathioprine, cyclophosphamide, and methotrexate; (98) musculoskeletal nonsteroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, ibuprofen, ketoprofen, ketorlac, and naproxen; (99) skeletal muscle relaxants, such as baclofen, cyclobenzaprine, and diazepam; (100) reverse neuromuscular blocker skeletal muscle relaxants, such as pyridostigmine; (101) neurological agents, such as nimodipine, riluzole, tacrine and ticlopidine; (102) anticonvulsants, such as carbamazepine, gabapentin, lamotrigine, phenytoin, and valproic acid; (103) barbiturate anticonvulsants, such as phenobarbital and primidone; (104) benzodiazepine anticonvulsants, such as clonazepam, diazepam, and lorazepam; (105) anti-parkinsonian agents, such as bromocriptine, levodopa, carbidopa, and pergolide; (106) anti-vertigo agents, such as meclizine; (107) opiate agonists, such as codeine, fentanyl, hydromorphone, methadone, and morphine; (108) opiate antagonists, such as naloxone; (109) β-blocker anti-glaucoma agents, such as timolol; (110) miotic anti-glaucoma agents, such as pilocarpine; (111) ophthalmic aminoglycoside anti-infectives, such as gentamicin, neomycin, and tobramycin; (112) ophthalmic quinolone anti-infectives, such as ciprofloxacin, norfloxacin, and ofloxacin; (113) ophthalmic corticosteroid anti-inflammatory agents, such as dexamethasone and prednisolone; (114) ophthalmic nonsteroidal anti-inflammatory drugs (NSAIDs), such as diclofenac; (115) antipsychotics, such as clozapine, haloperidol, and risperidone; (116) benzodiazepine anxiolytics, sedatives and hypnotics, such as clonazepam, diazepam, lorazepam, oxazepam, and prazepam; (117) psychostimulants, such as methylphenidate and pemoline; (118) antitussives, such as codeine; (119) bronchodilators, such as theophylline; (120) adrenergic agonist bronchodilators, such as albuterol; (121) respiratory corticosteroid anti-inflammatory agents, such as dexamethasone; (122) antidotes, such as flumazenil and naloxone; (123) heavy metal antagonists/chelating agents, such as penicillamine; (124) deterrent substance abuse agents, such as disulfiram, naltrexone, and nicotine; (125) withdrawal substance abuse agents, such as

bromocriptine; (126) minerals, such as iron, calcium, and magnesium; (127) vitamin B compounds, such as cyanocobalamin (vitamin B12) and niacin (vitamin B3); (128) vitamin C compounds, such as ascorbic acid; and (129) vitamin D compounds, such as calcitriol.

[00184] Further, recombinant or cell-derived proteins may be used, such as : recombinant beta-glucan; bovine immunoglobulin concentrate; bovine superoxide dismutase; the formulation comprising fluorouracil, epinephrine, and bovine collagen; recombinant hirudin (r-Hir), HIV-1 immunogen; recombinant human growth hormone (r-hGH); recombinant EPO (r-EPO); gene-activated EPO (GA-EPO); recombinant human hemoglobin (r-Hb); recombinant human mecasermin (r-IGF-1); recombinant interferon beta-1a; lenograstim (G-CSF); olanzapine; recombinant thyroid stimulating hormone (r-TSH); and topotecan.

[00185] Still further, the following listing of peptides, proteins, and other large molecules may also be used, such as interleukins 1 through 18, including mutants and analogues; interferons α, γ, and β; luteinizing hormone releasing hormone (LHRH) and analogues, gonadatropin releasing hormone (GnRH), transforming growth factor-α (TGF-α); fibroblast growth factor (FGF); tumor necrosis factor-α & γ (TNF-α and γ); nerve growth factor (NGF); growth hormone releasing factor (GHRF); epidermal growth factor (EGF); fibroblast growth factor homologous factor (FGFHF); hepatocyte growth factor (HGF); insulin growth factor (IGF); invasion inhibiting factor-2 (IIF-2); bone morphogenetic proteins 1-7 (BMP 1-7); somatostatin; thymosin-α-1; γ-globulin; superoxide dismutase (SOD); and complement factors.

[00186] The term "therapeutic agent" includes those agents that may be used for diagnostic purposes. Examples of such diagnostic agents include imaging agents that are capable of generating a detectable image shall include radionuclides and compounds containing them (e.g., tritium, iodine-125, iodine-131, iodine-123, iodine-124, astatine-210, carbon-11, carbon-14, nitrogen-13, fluorine-18, Tc-99m, Re-186, Ga-68, Re-188, Y-90, Sm-153, Bi-212, Cu-67, Cu-64, and Cu-62, to name a few), unpair spin atoms and free radicals (e.g., Fe, lanthanides, and Gd), contrast agents (e.g., chelated (DTPA) manganese), and fluorescent or chemiluminescent agents.

[00187] Various forms of the therapeutic agents may be used. These include, without limitation, such forms as uncharged molecules, molecular complexes, salts, ethers, esters, amides, and the like, which are biologically activated when implanted, injected or otherwise placed into a subject.

[00188] Plasticizers and stabilizing agents known in the art may be incorporated in polymers of the present invention. In certain embodiments, additives such as plasticizers and stabilizing agents are selected for their biocompatibility.

[00189] A composition of this invention may further contain one or more adjuvant substances, such as fillers, thickening agents or the like. In other embodiments, materials that serve as adjuvants may be associated with a subject composition, which may affect its characteristics. For example, fillers, such as bovine serum albumin (BSA) or mouse serum albumin (MSA), may be associated with a subject composition. In certain embodiments, the amount of filler may range from about 0.1 to about 50% or more by weight of the subject composition, or about 2.5, 5, 10, 25, 40 percent. Incorporation of such fillers may affect the biodegradation of the polymeric material and/or the sustained release rate of any encapsulated substance. Other fillers known to those of skill in the art, such as carbohydrates, sugars, starches, saccharides, celluoses and polysaccharides, including mannitose and sucrose, may be used in certain embodiments in the present invention.

[00190] In other embodiments, spheronization enhancers facilitate the production of subject compositions that are generally spherical in shape. Substances such as zein, microcrystalline cellulose or microcrystalline cellulose co-processed with sodium carboxymethyl cellulose may confer plasticity to the subject compositions as well as implant strength and integrity. In particular embodiments, during spheronization, extrudates that are rigid, but not plastic, result in the formation of dumbbell shaped implants and/or a high proportion of fines, and extrudates that are plastic, but not rigid, tend to agglomerate and form excessively large implants. In such embodiments, a balance between rigidity and plasticity is desirable. The percent of spheronization enhancer in a formulation depends on the other excipient characteristics and is typically in the range of 10-90% (w/w).

[00191] Buffers, acids and bases may be incorporated in the subject compositions to adjust their pH. Agents to increase the diffusion distance of agents released from a subject composition may also be included.

[00192] Disintegrants are substances which, in the presence of liquid, promote the disruption of the subject compositions. Disintegrants are most often used in implants, in which the function of the disintegrant is to counteract or neutralize the effect of any binding materials used in the subject formulation. In general, the mechanism of disintegration involves moisture absorption and swelling by an insoluble material. Examples of disintegrants include croscarmellose sodium and crospovidone that, in certain embodiments, may be incorporated into the subject compositions in the range of about 1-20% of total weight. In other cases, soluble fillers such as sugars (mannitol and lactose) also be added to facilitate disintegration of the subject compositions upon use.

[00193] Other materials may be used to advantage to control the desired release rate of a therapeutic agent for a particular treatment protocol. For example, if the sustained release is too slow for a particular application, a pore-forming agent may be added to generate additional pores in the composition. Any biocompatible water-soluble material may be used as the pore-forming agent. They may be capable of dissolving, diffusing or dispersing out of the formed polymer system whereupon pores and microporous channels are generated in the system. The amount of pore-forming agent (and size of dispersed particles of such pore-forming agent, if appropriate) within the composition should affect the size and number of the pores in the polymer system. Suitable pore-forming agents include, for example, sugars such as sucrose and dextrose, salts such as sodium chloride and sodium carbonate, and polymers such as hydroxylpropylcellulose, carboxymethylcellulose, polyethylene glycol, and polyvinylpyrrolidone. The size and extent of the pores may be varied over a wide range by changing the molecular weight and percentage of pore-forming agent incorporated into the polymer system.

[00194] The charge, lipophilicity or hydrophilicity of any subject composition may be modified by attaching in some fashion an appropriate compound to the surface of the composition. For example, surfactants may be used to enhance wettability of poorly

soluble or hydrophobic compositions. Examples of suitable surfactants include dextran, polysorbates and sodium lauryl sulfate. In general, surfactants are used in low concentrations, generally less than about 5%.

[00195] Binders are adhesive materials that may be incorporated in polymeric formulations to bind and maintain composition integrity. Binders may be added as dry powder or as solution. Sugars and natural and synthetic polymers may act as binders. Materials added specifically as binders are generally included in the range of about 0.5%-15% w/w of the subject composition. Certain materials, such as microcrystalline cellulose, also used as a spheronization enhancer, also have additional binding properties.

[00196] Various coatings may be applied to modify the properties of the subject compositions. Three exemplary types of coatings are seal, gloss and enteric coatings. Other types of coatings having various dissolution or erosion properties may be used to further modify subject matrices behavior, and such coatings are readily known to one of ordinary skill in the art.

[00197] The seal coat may prevent excess moisture uptake by the matrices during the application of aqueous based enteric coatings. The gloss coat generally improves the handling of the finished matrices. Water-soluble materials such as hydroxypropyl cellulose may be used to seal coat and gloss coat implants. The seal coat and gloss coat are generally sprayed onto the matrices until an increase in weight between about 0.5% and about 5%, often about 1% for a seal coat and about 3% for a gloss coat, has been obtained.

[00198] Enteric coatings consist of polymers which are insoluble in the low pH (less than 3.0) of the stomach, but are soluble in the elevated pH (greater than 4.0) of the small intestine. Polymers such as EUDRAGIT, RohmTech, Inc., Malden, Mass., and AQUATERIC, FMC Corp., Philadelphia, Penn., may be used and are layered as thin membranes onto the implants from aqueous solution or suspension or by a spray drying method. The enteric coat is generally sprayed to a weight increase of about one to about 30%, or for example, about 10 to about 15% and may contain coating adjuvants such as plasticizers, surfactants, separating agents that reduce the tackiness of the implants during coating, and coating permeability adjusters.

[00199] The present compositions may additionally contain one or more optional additives such as fibrous reinforcement, colorants, perfumes, rubber modifiers, modifying agents, etc. In practice, each of these optional additives should be compatible with the resulting polymer and its intended use. Examples of suitable fibrous reinforcement include PGA microfibrils, collagen microfibrils, cellulosic microfibrils, and olefinic microfibrils. The amount of each of these optional additives employed in the composition is an amount necessary to achieve the desired effect.

C. Physical structures of the subject compositions

[00200] The subject polymers may be formed in a variety of shapes. For example, in certain embodiments, subject polymer matrices may be presented in the form of microparticles or nanoparticles. Such particles may be prepared by a variety of methods known in the art, including for example, solvent evaporation, spray-drying or double emulsion methods.

[00201] The shape of microparticles and nanoparticles may be determined by scanning electron microscopy. Spherically shaped nanoparticles are used in certain embodiments for circulation through the bloodstream. If desired, the particles may be fabricated using known techniques into other shapes that are more useful for a specific application.

[00202] In addition to intracellular delivery of a therapeutic agent, it also possible that particles of the subject compositions, such as microparticles or nanoparticles, may undergo endocytosis, thereby obtaining access to the cell. The frequency of such an endocytosis process will likely depend on the size of any particle.

[00203] In certain embodiments, solid articles useful in defining shape and providing rigidity and structural strength to the polymeric matrices may be used. For example, a polymer may be formed on a mesh or other weave for implantation.

[00204] The mechanical properties of the polymer may be important for the processability of making molded or pressed articles for implantation. For example, the glass transition temperature may vary widely but must be sufficiently lower than the

temperature of decomposition to accommodate conventional fabrication techniques, such as compression molding, extrusion or injection molding.

D. Biodegradability and release characteristics

[00205] In certain embodiments, the polymers of the present invention, upon contact with body fluids, undergo gradual degradation.

[00206] If a subject polymer is formulated with a biologically active agent or other material, release of such a biologically active agent or other material for a sustained or extended period as compared to the release from an isotonic saline solution generally results. Such release profile may result in prolonged delivery (over, say 1 to about 5,000 hours, or alternatively about 4 to about 1500 hours) of effective amounts (e.g., about 0.00001 mg/kg/hour to about 10 mg/kg/hour) of the biologically active agent or any other material associated with the polymer.

[00207] A variety of factors may affect the desired rate of hydrolysis of polymers of the subject invention, the desired softness and flexibility of the resulting composition, rate and extent of bioactive material release. Some of such factors include: the selection of the various substituent groups, such as the phosphate group making up the linkage in the polymer backbone (or analogs thereof), the enantiomeric or diastereomeric purity of the monomeric subunits, homogeneity of subunits found in the polymer, and the length of the polymer. For instance, the present invention contemplates heteropolymers with varying linkages, and/or the inclusion of other monomeric elements in the polymer, in order to control, for example, the rate of biodegradation.

[00208] To illustrate further, a wide range of degradation rates may be obtained by adjusting the hydrophobicities of the backbones or side chains of the polymers while still maintaining sufficient biodegradability for the use intended for any such polymer. Such a result may be achieved by varying the various functional groups of the polymer. For example, the combination of a hydrophobic backbone and a hydrophilic linkage produces heterogeneous degradation because cleavage is encouraged whereas water penetration is resisted. In another example, it is expected that use of substituent on phosphate in the polymers of the present invention that is lipophilic, hydrophobic or bulky group would slow the rate of degradation. For example, it is expected that conversion of the phosphate

side chain to a more lipophilic, more hydrophobic or more sterically bulky group would slow down the rate of biodegradation. Thus, release is usually faster from polymer compositions with a small aliphatic group side chain than with a bulky aromatic side chain.

[00209] One protocol generally accepted in the field that may be used to determine the release rate of any therapeutic agent or other material loaded in the polymer matrices of the present invention involves degradation of any such composition in a 0.1 M PBS solution (pH 7.4) at 37 °C, an assay known in the art. For purposes of the present invention, the term "PBS protocol" is used herein to refer to such protocol.

[00210] In certain instances, the release rates of different polymer systems of the present invention may be compared by subjecting them to such a protocol. In certain instances, it may be necessary to process polymeric systems in the same fashion to allow direct and relatively accurate comparisons of different systems to be made. For example, the present invention teaches several different means of formulating the polymeric matrices of the present invention. Such comparisons may indicate that any one polymeric system releases incorporated material at a rate from about 2 or less to about 1000 or more times faster than another polymeric system. Alternatively, a comparison may reveal a rate difference of about 3, 5, 7, 10, 25, 50, 100, 250, 500 or 750. Even higher rate differences are contemplated by the present invention and release rate protocols.

[00211] In certain embodiments, when formulated in a certain manner, the release rate for polymer systems of the present invention may present as mono- or bi-phasic. Release of any material incorporated into a subject composition, which is often provided as a microsphere, may be characterized in certain instances by an initial increased release rate, which may release from about 5 to about 50% or more of any incorporated material, or alternatively about 10, 15, 20, 25, 30 or 40%, followed by a release rate of lesser magnitude.

[00212] The release rate of any incorporated material may also be characterized by the amount of such material released per day per mg of subject composition. For example, in certain embodiments, the release rate may vary from about 1 μg or less of any incorporated material per day per mg of polymeric system to about 5000 or more

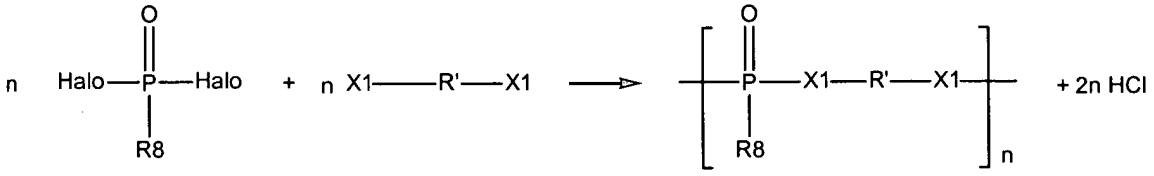
μg/day/mg. Alternatively, the release rate may be about 10, 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800 or 900 μg/day/mg. In still other embodiments, the release rate of any incorporated material may be 100 μg/day/mg or even higher. In certain instances, materials incorporated and characterized by such release rate protocols may include therapeutic agents, fillers, and other substances.

[00213] In another aspect, the rate of release of any material from any subject composition may be presented as the half-life of such material in such composition.

[00214] In addition to the embodiment involving protocols for in vitro determination of release rates, in vivo protocols, whereby in certain instances release rates for polymeric systems may be determined in vivo, are also contemplated by the present invention. Other assays useful for determining the release of any material from the polymers of the present system are known in the art.

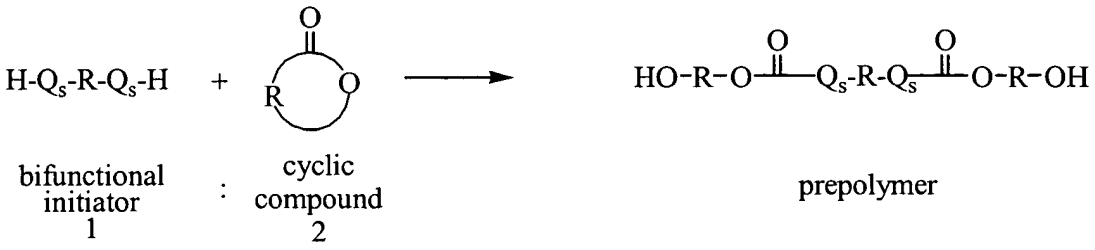
4. Exemplary methods of making the subject compositions

[00215] In general, the polymers of the present invention may be prepared by melt polycondensation, solution polymerization or interfacial polycondensation. Techniques necessary to prepare the subject polymers are known in the art, and reference is made in particular to U.S. Provisional Application Serial No. 60/216,462 filed July 6, 2000, U.S. Provisional Application Serial No. 60/228,729 filed August 29, 2000, and U.S. Application 09/885,085 filed June 21, 2000. The most common general reaction in preparing the compositions is a dehydrochlorination between a phosphodichloridate and a diol according to the following equation:

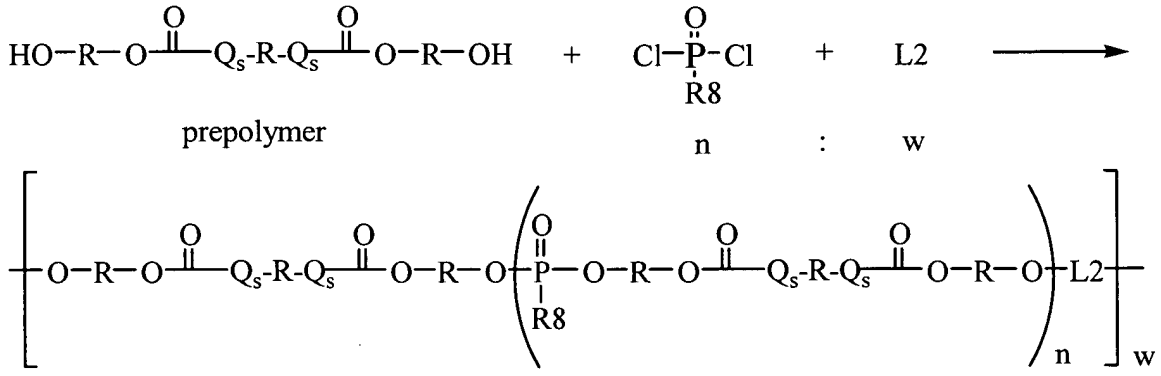


[00216] Certain of the subject polymers may be obtained by condensation between appropriately substituted dichlorides and diols.

[00217] In certain embodiments, a prepolymer is first prepared as one component of the biocompatible polymer by ring opening polymerization of a cyclic compound with a bifunctional initiator.



where Qs is defined as before and R represents a chemical moiety that does not materially interfere with the biocompatibility of the polymer. The prepolymer is then reacted in a two step process with a phosphorous compound and L2 where the phosphorous compound, L2, n, and w are defined as before.



[00218] An advantage of melt polycondensation is that it avoids the use of solvents and large amounts of other additives, thus making purification more straightforward. This method may also provide polymers of reasonably high molecular weight. Somewhat rigorous conditions, however, are often required and may lead to chain acidolysis (or hydrolysis if water is present). Unwanted, thermally induced side reactions, such as cross-linking reactions, may also occur if the polymer backbone is susceptible to hydrogen atom abstraction or oxidation with subsequent macroradical recombination.

[00219] To minimize these side reactions, the polymerization may also be carried out in solution. Solution polycondensation requires that both the prepolymer and the phosphorus component be sufficiently soluble in a common solvent. Typically, a

chlorinated organic solvent is used, such as chloroform, dichloromethane or dichloroethane. The solution polymerization is generally run in the presence of equimolar amounts of the reactants. For example, there may be present an excess of an acid acceptor and a catalyst, such as 4-dimethylaminopyridine (DMAP). Useful acid acceptors include tertiary amines as pyridine or triethylamine. The product is then typically isolated from the solution by precipitation in a non-solvent and purified to remove the hydrochloride salt by conventional techniques known to those of ordinary skill in the art, such as by washing with an aqueous acidic solution, e.g., dilute HCl.

[00220] Reaction times tend to be longer with solution polymerization than with melt polymerization. However, because overall milder reaction conditions may be used, side reactions are minimized, and more sensitive functional groups may be incorporated into the polymer. The disadvantages of solution polymerization are that removal of solvents may be difficult.

[00221] Interfacial polycondensation may be used when high molecular-weight polymers are desired at high reaction rates. By such methods, mild conditions minimize side reactions, and the dependence of high molecular weight on stoichiometric equivalence between diol and dichloridate inherent in solution methods is removed. However, hydrolysis of the acid chloride may occur in the alkaline aqueous phase, and sensitive dichloridates that have some solubility in water are generally subject to hydrolysis rather than polymerization. Phase transfer catalysts, such as crown ethers or tertiary ammonium chloride, may be used to bring the ionized diol to the interface to facilitate the polycondensation reaction. The yield and molecular weight of the resulting polymer after interfacial polycondensation are affected by reaction time, molar ratio of the monomers, volume ratio of the immiscible solvents, the type of acid acceptor, and the type and concentration of the chase transfer catalyst.

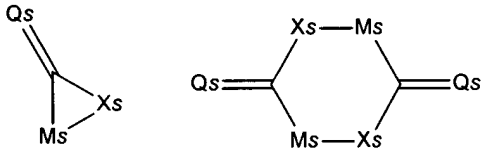
[00222] Methods for making the present invention may take place at widely varying temperatures, depending upon whether a solvent is used and, if so, which one; the molecular weight desired; the susceptibility of the reactants to form side reactions; and the presence of a catalyst. Usually, the process takes place at a temperature ranging from about 0 to about +235 °C for melt conditions. Somewhat lower temperatures, e.g.,

for example from about -50 to about 100 °C, may be possible with solution polymerization or interfacial polycondensation with the use of either a cationic or anionic catalyst.

[00223] The time required for the process may vary widely, depending on the type of reaction being used, the molecular weight desired and, in general, the need to use more or less rigorous conditions for the reaction to proceed to the desired degree of completion. Typically, however, the synthetic process takes place during a time between about 30 minutes and about 7 days.

[00224] Although the process may be in bulk, in solution, by interfacial polycondensation, or any other convenient method of polymerization, in many instant embodiments, the process takes place under solution conditions. Particularly useful solvents include methylene chloride, chloroform, tetrahydrofuran, di-methyl formamide, dimethyl sulfoxide or any of a wide variety of inert organic solvents.

[00225] In greater detail, prepolymers such as the DABHET prepolymer may be prepared, at least in part, by reacting a compound having a formula H-Y1-L3-Y1-H, such as 2-aminoethanol, ethylene glycol, ethane dithiol, bis(2-hydroxyethyl)terephthalate, etc., with a cyclic compound, e.g., having one of the following structures: for example, caprolactone or lactide (lactic acid dimer).

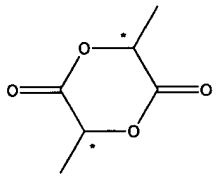
[00226] 

[00227] Thus, the cyclic compound may include one or two subunits ts. For cyclic compounds containing two subunits, the two subunits contained therein may be the same or different.

[00228] For synthesizing, for example, a prepolymer of the current invention, wherein x and y are on average about 2, an equivalent of ethylene glycol as H-Y1-L1-Y1-H may be reacted with 4 equivalents of

[00229] 

[00230] or 2 equivalents of

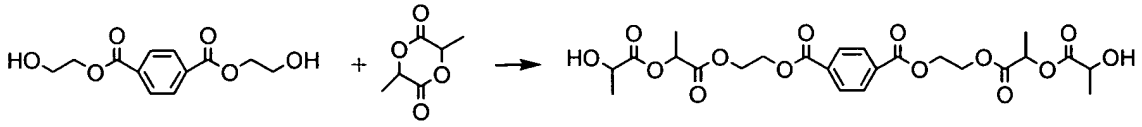


[00231]

because lactic acid dimer contains two monomer units for each equivalent of the cyclic compound. Variation of the ratio of cyclic compound to ethylene glycol or other bifunctional core will likewise vary the values of x and y, although x and y will be substantially equal for a symmetrical bifunctional core (e.g., ethylene glycol) for subject prepolymers prepared by this method. For an unsymmetrical bifunctional core (e.g., 2-aminoethanol), the ratio of x:y may vary considerably, as will be understood by one of skill in the art and may be determined without undue experimentation.

[00232] Polymers of the present invention may generally be isolated from the reaction mixture by conventional techniques, such as by precipitating out, extraction with an immiscible solvent, evaporation, filtration, crystallization and the like. Typically, the subject polymers are both isolated and purified by quenching a solution of polymer with a non-solvent or a partial solvent, such as diethyl ether or petroleum ether.

[00233] A more detailed reaction scheme to prepare one exemplary composition of the present invention is as follows:

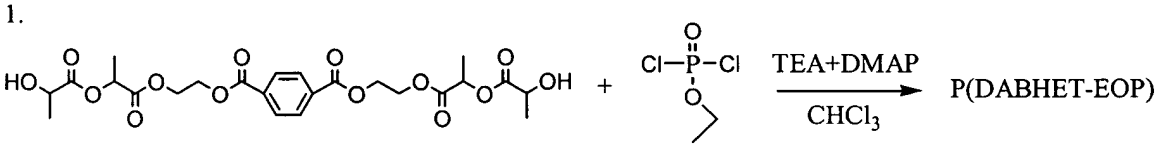


BHET : DA

DABHET prepolymer

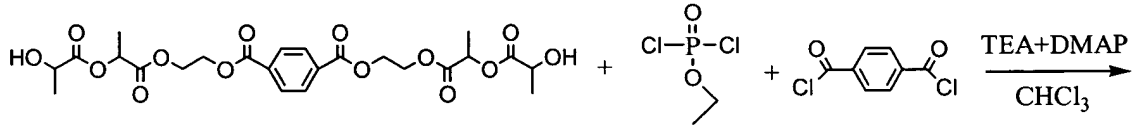
DA:BHET = 2:1

1.



DABHET prepolymer EOP

2.



P(DABHET-EOP/TC) polymer

5. Dosages and formulations of the subject compositions

[00234] In most embodiments, the subject polymers will incorporate the substance to be delivered in an amount sufficient to deliver to a patient a therapeutically effective amount of an incorporated therapeutic agent or other material as part of a prophylactic or therapeutic treatment. The desired concentration of active compound in a subject composition will depend on absorption, inactivation, and excretion rates of the drug as well as the delivery rate of the compound from the composition. It is to be noted that dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. Typically, dosing will be determined using techniques known to one skilled in the art.

[00235] Formulations of the subject compositions may be prepared by conventional means known to those of skill in art.

[00236] The invention further provides kits for use in treating a disease or condition. For example, the kit may comprise a subject polymer and a therapeutic agent, either already combined or provided separately. The composition may be packaged in a suitable container. The kit may further comprise instructional materials for using the kit.

[00237] Toxicity and therapeutic efficacy of subject compositions may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 and the ED50. Compositions may exhibit large therapeutic indices. Although compositions that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets the active agent to the desired site in order to reduce side effects.

[00238] In another aspect of the invention, the efficacy of treatment using the subject compositions may be compared to treatment regimens known in the art in which the therapeutic agent in question is not encapsulated within a subject polymer or other treatment regimens. The metrics by which such comparison may be made include survival rates, life expectancy, size of a tumor or neoplasm, rate of growth of a tumor or neoplasm, number of infections, and other metrics known to those of skill in the art and appropriate to the disease or condition being treated. In certain embodiments, the improvement observed for any of such metrics upon treatment with a subject composition as compared to treatment with the same active agent in the such composition absent the subject polymer in such composition may be about 25%, 50% 75%, 100% as effective, or 2, 2, 5, 10, 20, 50, 100, 250 or more times as effective.

EXEMPLIFICATION

[00239] The invention now being generally described, it will be more readily understood by reference to the following examples which are included merely for purposes of illustration of certain aspects and embodiments of the present invention, and are not intended to limit the invention.

[00240] Chemicals:

[00241] D, L-lactide was purchased from Purac America with >99.5% purity.

[00242] BHET was purchased from Sigma-Aldrich with 95% purity.

[00243] EOP was purchased from Rhodia Inc. with 99.1% purity.

[00244] TEA was purchased from Sigma-Aldrich with 99.5% purity.

[00245] DMAP was purchased from Reilly Industries Inc. with 99% purity.

[00246] Chloroform was purchased from Sigma-Aldrich with 99+% anhydrous grade.

[00247] Example 1: Synthesis DABHET Prepolymer

[00248] 5.03 g of BHET and 6.16g D, L lactide were charged in a 250mL round bottom flask equipped with a stir bar. The r.b. flask was applied with vacuum and exchanged with nitrogen several times to remove the air inside. The reaction vessel was then placed in a 135°C oil bath. When the reactants were completely melted, 500 ppm of stannous octoate was added. The reaction was kept at 135°C for 17 hours.

[00249] Example 2: Synthesis of P(DABHET-EOP) (Reaction 1)

[00250] 11.19g of DABHET prepolymer from Example 1 was dissolved in chloroform. 4.61g of TEA and 0.63g of DMAP were used as the acid acceptors and catalyst. 3.29g of EOP was added gradually to the DABHET solution in chloroform at –10°C to –15°C. After EOP addition was completed, the reaction solution was brought to room temperature and stirred overnight. The next day, the reaction mixture was purified by filtration and ion exchange resin treatment. Finally, the polymer solution was precipitated in the ether and petroleum ether mixture.

[00251] Example 3: Synthesis of P(DABHET-EOP/TC) (Reaction 2)

[00252] 11.11 g of DABHET prepolymer from example 1 was dissolved in chloroform. 4.56g of TEA and 0.60g of DMAP were added.. 2.63g of EOP was added gradually to the DABHET solution in chloroform at –10°C to –15°C. After f EOP addition was completed, the reaction solution was brought to room temperature and stirred for 1-2 hours. The terephthaloyl chloride (TC) was added gradually to the reaction mixture at

[00253] −10°C to −15°C. The reaction solution was brought to room temperature again and stirred overnight. The next day, the reaction mixture was purified by filtration and ion exchange resin treatment. Finally, the polymer solution was precipitated in the ether and petroleum ether mixture (1:3, v/v).

[00254] A BHET:D,L-LA = 1:2 ratio was used for the initial reactions. The molar ratios among BHET, EOP, and TC were varied as 100/80/20, 100/85/15, 100/90/10, and 100/95/5, respectively.

Composition	Mw (KD)	Mn (KD)	PD	Tg (^{0}C)
P (DABHET-EOP)	18.1	13.62	1.33	16
P (DABHET-EOP/TC, 75/25)	16.3	11.6	1.4	27
P (DABHET-EOP/TC, 80/20)	58.6	34.17	1.71	26
P (DABHET-EOP/TC, 80/20)	77.79	35.77	2.17	30
P (DABHET-EOP/TC, 80/20)	39.0	27.2	1.41	
P (DABHET-EOP/TC, 85/15)	15.37*	10.29	1.49	NA
P (DABHET-EOP/TC, 85/15)	15.6	11.8	1.3	28
P (DABHET-EOP/TC, 90/10)	16.7	11.8	1.42	21
P (DABHET-EOP/TC, 90/10)	15.49*	10.75	1.44	NA
P (DABHET-EOP/TC, 95/5)	17.5	12	1.46	16

*The GPC data of these two batches were measured before the purification step.

EQUIVALENTS

[00255] While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification. The

full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[00256] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, parameters, descriptive features and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention.

[00257] All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

[00258] Also incorporated by reference are the following patents:

US 6,166,173, US 6,153,212, US 6,322,797.